

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing  
(day/month/year) 18.10.2000

Applicant's or agent's file reference  
379-110PCT

IMPORTANT NOTIFICATION

International application No.  
PCT/CA99/00311

International filing date (day/month/year)  
19/04/1999

Priority date (day/month/year)  
17/04/1998

Applicant  
CURRY, Kenneth et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>379-110PCT</b>		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. <b>PCT/CA99/00311</b>	International filing date (day/month/year) <b>19/04/1999</b>	Priority date (day/month/year) <b>17/04/1998</b>	
International Patent Classification (IPC) or national classification and IPC <b>C07C229/28</b>			
Applicant <b>CURRY, Kenneth et al.</b>			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 47 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input checked="" type="checkbox"/> Certain documents cited</p> <p>VII <input checked="" type="checkbox"/> Certain defects in the international application</p> <p>VIII <input checked="" type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand <b>17/11/1999</b>		Date of completion of this report <b>18.10.2000</b>	
Name and mailing address of the international preliminary examining authority:  <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>		Authorized officer  <b>Butkowsky-Walkiw, T</b>  Telephone No. +49 89 2399 9594 	

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/CA99/00311

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

37,38	as originally filed		
1-7,9,10,16-30, 32-36	as received on	28/07/1999 with letter of	09/07/1999
8,11,11a,12-15, 31	as received on	20/07/2000 with letter of	20/07/2000

**Claims, No.:**

1-21	as received on	20/07/2000 with letter of	20/07/2000
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**Drawings, sheets:**

1	as received on	28/07/1999 with letter of	09/07/1999
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2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

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EXAMINATION REPORT**

International application No. PCT/CA99/00311

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Yes: Claims 1-21
	No: Claims
Inventive step (IS)	Yes: Claims 1-21
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-6,8-13,18-21
	No: Claims

**2. Citations and explanations**

see separate sheet

**VI. Certain documents cited****1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)**

see separate sheet

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

see separate sheet

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet



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**EXAMINATION REPORT - SEPARATE SHEET**

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**V.**

In the light of the documents cited in the search report the present claims 1-21 can be considered as being novel (Art. 33(2) PCT).

Further, the present claims 1-21 can be considered as being inventive (Art. 33(3) PCT) as the object of the present application, namely to provide compounds that demonstrate activity at the various metabotropic glutamate receptors (mGluRs), and the presently claimed solution have not been suggested by any of the cited prior art documents. D1 (PELLICCIARI et al, Asymmetric Synthesis of Enantiomerically pure (2S,1'S,2'S,3'R)-Phenylcarboxycyclopropylglycine, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 18, pages 2243-2246, 1996) which can be considered as closest prior art document refers to cyclopropyl analogs and in the light of this teaching it was not obvious for a skilled person to arrive at the present subject-matter.

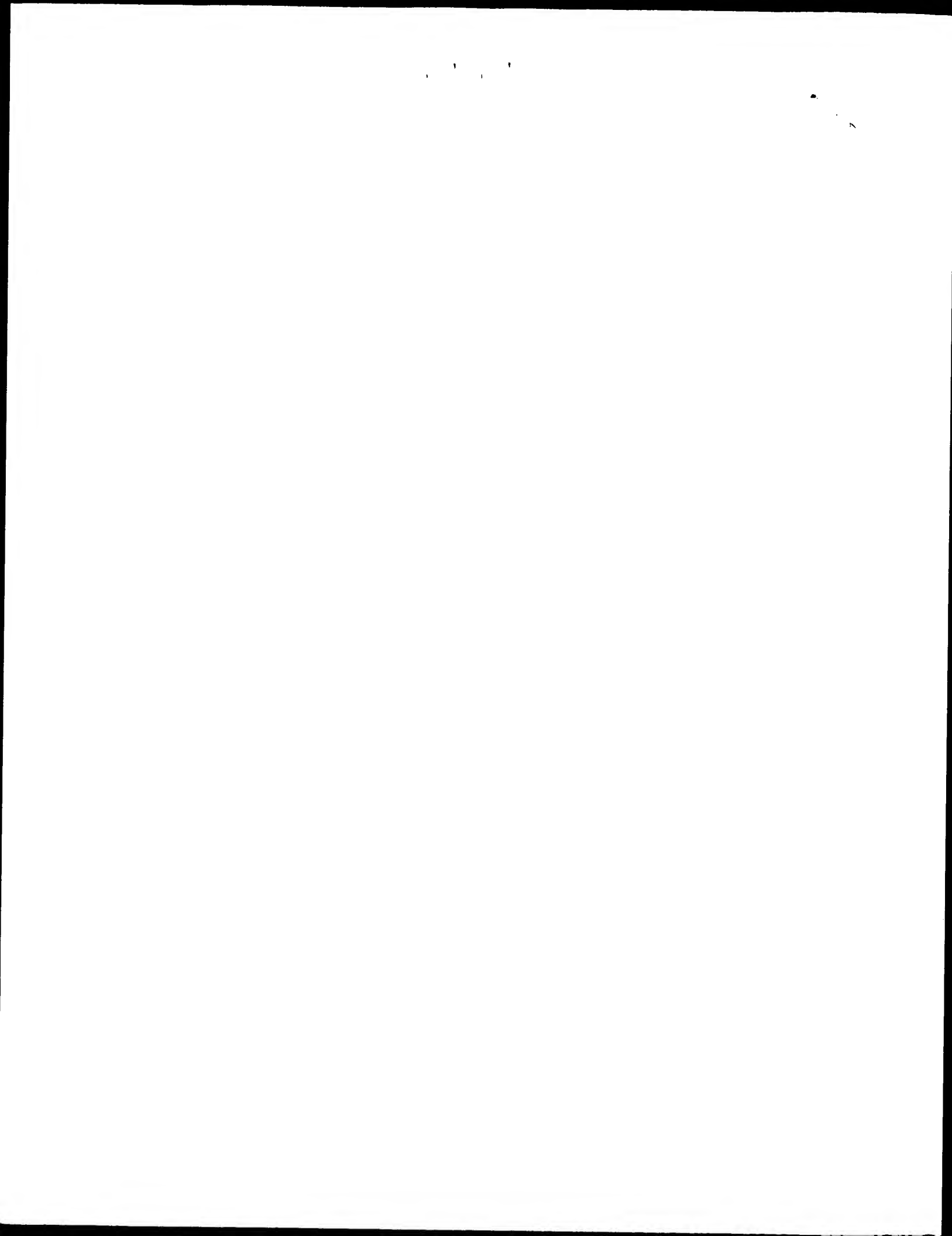
For the assessment of the present claims 7,14-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**VI.**

The present application claims priority rights from 17/4/98. The priority document pertaining to the present application was not available at the time of establishing this report. Hence it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D2 (PELLICCIARI et al: "Synthesis and preliminary evaluation of (S)-2-(4'-carboxycubyl)glycine, a new selective mGluR1 antagonist" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 12, 16/8/98, pages 1569-1574), cited in the search report would become very relevant in the assessment of the patentability of the present application.

**VII.**

The amendments in on pages 8,11,12,14 and claims 4,5,13,16,17 and 21 filed with the letter dated 20/7/00 introduce subject-matter which extends beyond the content of the



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**EXAMINATION REPORT - SEPARATE SHEET**

application as filed, contrary to Article 34(2)(b) PCT.

**VIII.**

The term "aliphatic" (claim 1) without any indication of the number of carbon atoms is too broad in scope and therefore unclear (Art. 6 PCT).

Further, expressions as "the like" and "about" with reference to ranges are unclear.





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## CUBANE ANALOGS WITH ACTIVITY AT THE METABOTROPIC GLUTAMATE RECEPTORS

### FIELD OF THE INVENTION

This invention pertains to therapeutically active cubane derivatives, a method for preparing the same, pharmaceutical compositions comprising the compounds and a method of treating diseases of the Central Nervous System (CNS) therewith.

### BACKGROUND OF THE INVENTION

The acidic amino acid L-Glutamate is recognized as the major excitatory neurotransmitter in the CNS. The receptors that respond to L-Glutamate are called excitatory amino acid receptors. The excitatory amino acid receptors are thus of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiratory and cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types and both are activated by L-Glutamic acid and its analogs. Receptors activated by L-Glutamic acid that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic." This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists N-Methyl-D-aspartate (NMDA),  $\alpha$ -Amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and Kainic acid (KA).

The second general type of receptor is the G-protein or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D, increases or decreases in cAMP formation, and changes in ion channel function (Schoepp and Conn, *Trends in Pharmacological Science*, 14:13, 1993). Both types of receptors appear not only to mediate normal synaptic transmission along excitatory pathways but also to participate in the modification of synaptic connections during development and throughout life.

So far eight different clones of the G-protein-coupled metabotropic glutamate receptors (mGluRs) have been identified (Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426). These receptors function to modulate the presynaptic release of L-Glutamate, and the postsynaptic



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sensitivity of the neuronal cell to L-Glutamate excitation. Based on pharmacology, sequence homology and the signal transduction pathway that they activate, the mGluRs have been subclassified into three groups. The mGluR1 and mGluR5 receptors form group I. They are coupled to hydrolysis of phosphatidylinositol (PI) and are selectively activated by (RS)-3,5-dihydroxyphenylglycine (Brabet et al., *Neuropharmacology*, 34, 895-903, 1995). Group II comprises mGluR<sub>2</sub> and mGluR<sub>3</sub> receptors. They are negatively coupled to adenylate cyclase and are selectively activated by (2S,1'R,2'R,3'R)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV; Hayashi et al., *Nature*, 366, 687-690, 1993). Finally, the mGluR<sub>4</sub>, mGluR<sub>6</sub>, mGluR<sub>7</sub>, and mGluR<sub>8</sub> receptors belong to group III. They are also negatively coupled to adenylate cyclase and are selectively activated by (L)-2-amino-4-phosphonobutyric acid (L-AP4; Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426).

Agonists and antagonists of these receptors are believed useful for the treatment of acute and chronic neurodegenerative conditions, and as antipsychotic, anticonvulsant, analgesic, anxiolytic, antidepressant, and anti-emetic agents. Antagonists and agonists of neural receptors are classified as selective for a particular receptor or receptor subtype, or as non-selective. Antagonists may also be classified as competitive or non-competitive. While competitive and non-competitive antagonists act on the receptors in a different manner to produce similar results, selectivity is based upon the observations that some antagonists exhibit high levels of activity at a single receptor type, and little or no activity at other receptors. In the case of receptor-specific diseases and conditions, the selective agonists and antagonists are of the most value.

Compounds such as L-Glutamic acid, Quisqualic acid and Ibotenic acid are known to act as non-selective agonists on the mGluRs, while selective ionotropic glutamate receptor agonists such as NMDA, AMPA and Kainic acid have little effect on these receptors. Recently a few compounds without activity at the ionotropic glutamate receptors but with activity at the metabotropic receptors have been identified. These include *trans*-ACPD (*trans* (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid), the partial agonist L-AP3 (L-2-amino-3-phosphonopropionic acid, Palmer, E., Monaghan, D. T. and Cotman, C. W. *Eur. J. Pharmacol.* 166, 585-587, 1989; Desai, M. A. and Conn, P. J. *Neuroscience Lett.* 109, 157-162, 1990; Schoepp, D. D. et al., *J. Neurochemistry*, 56, 1789-1796, 1991; Schoepp D. D. and Johnson B. G. *J. Neurochemistry* 53, 1865-1613, 1989), L-AP4 (L-2-amino-4-phosphonobutyric acid) which is an agonist at the mGluR<sub>4</sub> receptor (Thomsen C. et al., *Eur. J. Pharmacol.* 227, 361-362, 1992) and some of the isomers of CCG (2-(carboxycyclopropyl)glycines) especially L-CCG-I and L-CCG-II (Hayashi, Y. et al., *Br. J. Pharmacol.* 107, 539-543, 1992)



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Very few selective antagonists at the mGluRs have been reported. However some phenylglycine derivatives, *S*-4CPG (*S*-4-carboxyphenylglycine), *S*-4C3HPG (*S*-4-carboxy -3-hydroxyphenylglycine) and *S*-MCPG (*S*- $\alpha$ -methyl-4-carboxyphenylglycine) have been reported to antagonize *trans*-ACPD- stimulated phosphoinositide hydrolysis and thus possibly act as antagonists at mGluR<sub>1</sub> and mGluR<sub>5</sub> subtypes (Thomsen, C. and Suzdak, P, *Eur. J. Pharmacol.* 245, 299, 1993).

Research directed towards mGluRs is beginning to show that mGluRs may be implicated in a number of normal as well as pathological mechanisms in the brain and spinal cord. For example, activation of these receptors on neurons can: influence levels of alertness, attention and cognition; protect nerve cells from excitotoxic damage resulting from ischemia, hypoglycemia and anoxia; modulate the level of neuronal excitation; influence central mechanisms involved in controlling movement; reduce sensitivity to pain; reduce levels of anxiety.

The use of compounds active at the mGluRs for the treatment of epilepsy is corroborated by investigations of the influence of *trans*-ACPD on the formation of convulsions (Sacaan and Schoepp, *Neuroscience Lett.* 139, 77, 1992) and that phosphoinositide hydrolysis mediated via mGluR is increased after kindling experiments in rats (Akiyama et al. *Brain Res.* 569, 71, 1992).

*Trans*-ACPD has been shown to increase release of dopamine in the rat brain, which indicates that compounds acting on the mGluRs might be usable for the treatment of Parkinson's disease and Huntington's Chorea (Sacaan et al., *J. Neurochemistry* 59, 245, 1992).

*Trans*-ACPD has also been shown to be a neuroprotective agent in a medial cerebral artery occlusion (MCAO) model in mice (Chiamulera et al. *Eur. J. Pharmacol.* 215, 353, 1992), and it has been shown to inhibit NMDA-induced neurotoxicity in nerve cell cultures (Koh et al., *Proc. Natl. Acad. Sci. USA* 88, 9431, 1991). The mGluR-active compounds are also implicated in the treatment of pain. This is proved by the fact that antagonists at the metabotropic glutamate receptors antagonize sensory synaptic response to noxious stimuli of thalamic neurons (Eaton, S. A. et al., *Eur. J. Neuroscience*, 5, 186, 1993).

The use of compounds active at the mGluRs for treatment of neurological diseases such as senile dementia have also been indicated by the findings of Zheng and Gallagher (*Neuron* 9, 163, 1992) and Bashir et al. (*Nature* 363, 347, 1993) who demonstrated that activation of mGluRs is necessary for the induction of long-term potentiation (LTP) in nerve cells (septal nucleus, hippocampus) and the finding that long-term depression is induced after activation of metabotropic glutamate receptors in cerebellar granule cells (Linden et al. *Neuron* 7, 81, 1991).



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Thus compounds that demonstrate either activating or inhibiting activity at mGluRs have therapeutic potential for the treatment of neurological disorders. These compounds have application as new drugs to treat both acute and chronic neurological disorders, such as stroke and head injuries; epilepsy; movement disorders associated with Parkinson's disease and Huntington's chorea; pain; anxiety; AIDS dementia; and Alzheimer's disease. Since the mGluRs can influence levels of alertness, attention and cognition; protect nerve cells from excitotoxic damage resulting from ischemia, hypoglycemia and anoxia; modulate the level of neuronal excitation; influence central mechanisms involved in controlling movement; reduce sensitivity to pain; and reduce levels of anxiety, these compounds can also be used to influence these situations and also find use in learning and memory deficiencies such as senile dementia. mGluRs may also be involved in addictive behavior, alcoholism, drug addiction, sensitization and drug withdrawal (*Science*, 280:2045, 1998), so compounds acting at mGluRs might also be used to treat these disorders.

The current pharmaceutical options for treating neurological disorders tend to be very general and non-specific in their actions in that, although they may reduce the clinical symptoms associated with a specific neurological disorder, they may also negatively impact normal function of the central nervous system of patients. Thus new cellular targets and drugs that are more specific in their actions require to be identified and developed and thus a need remains for chemical compounds that demonstrate specific binding characteristics towards mGluRs.

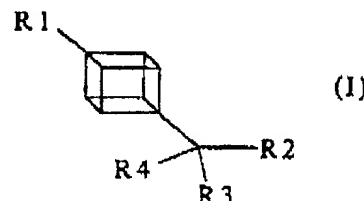




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## SUMMARY OF THE INVENTION

It is an object of this invention to provide novel compounds that demonstrate activity at the various metabotropic glutamate receptors (mGluRs). In particular, a compound of Formula I and stereoisomers thereof:



wherein:

R1 can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfinio, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, -CH<sub>2</sub>-isoxazol and higher homologues thereof;

R2 can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea,

R3 can be H, aliphatic, aromatic or heterocyclic,

R4 can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol;

and pharmaceutically acceptable salts thereof.

## DETAILED DESCRIPTION OF THE INVENTION

The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius, "N" refers to normal or normality; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "mL" means milliliter or milliliters; "M" refers to molar or molarity, "MS" refers to mass spectrometry, "IR"



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refers to infrared spectroscopy; and "NMR" refers to nuclear magnetic resonance spectroscopy.

As would be understood by the skilled artisan throughout the synthesis of the compounds of Formula I, it may be necessary to employ an amino-protecting group or a carboxy-protecting group in order to reversibly preserve a reactively susceptible amino or carboxy functionality while reacting other functional groups on the compound.

Examples of such amino-protecting groups include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, *t*-butoxycarbonyl, 2-(4-xenyl)-isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxy-carbonyl, 1-methylcyclopentanyloxy-carbonyl, cyclohexanyloxy-carbonyl, 1-methylcyclohexanyloxy-carbonyl, 2-methylcyclohexanyloxy-carbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; benzoylmethylsulfonyl group, 2-nitrophenylsulfenyl, diphenylphosphine oxide and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino-protecting group(s). Preferred amino-protecting groups are *t*-butoxycarbonyl (*t*-Boc), allyloxycarbonyl and benzyloxycarbonyl (CbZ). Further examples of these groups are found in E. Haslam in *Protective Groups in Organic Synthesis*; McOmie, J. G. W., Ed. 1973, at Chapter 2; and Greene, T. W. and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, Second edition; Wiley-Interscience: 1991; Chapter 7.

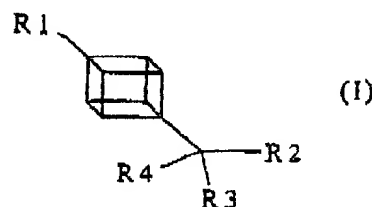
Examples of such carboxyl-protecting groups include methyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, *t*-butyl, *t*-amyl, trityl,



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4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4''-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, *t*-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl,  $\beta$ -(di(*n*-butyl)methylsilyl)ethyl, *p*-toluenesulfonyl, 4-nitrobenzylsulfonyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl and like moieties. Preferred carboxyl-protecting groups are allyl, benzyl and *t*-butyl. Further examples of these groups are found in E. Haslam, *supra*, at Chapter 5; and T. W. Greene and P. G. M. Wuts, *supra*, at Chapter 5.

The present invention provides a compound of the formula:



wherein:

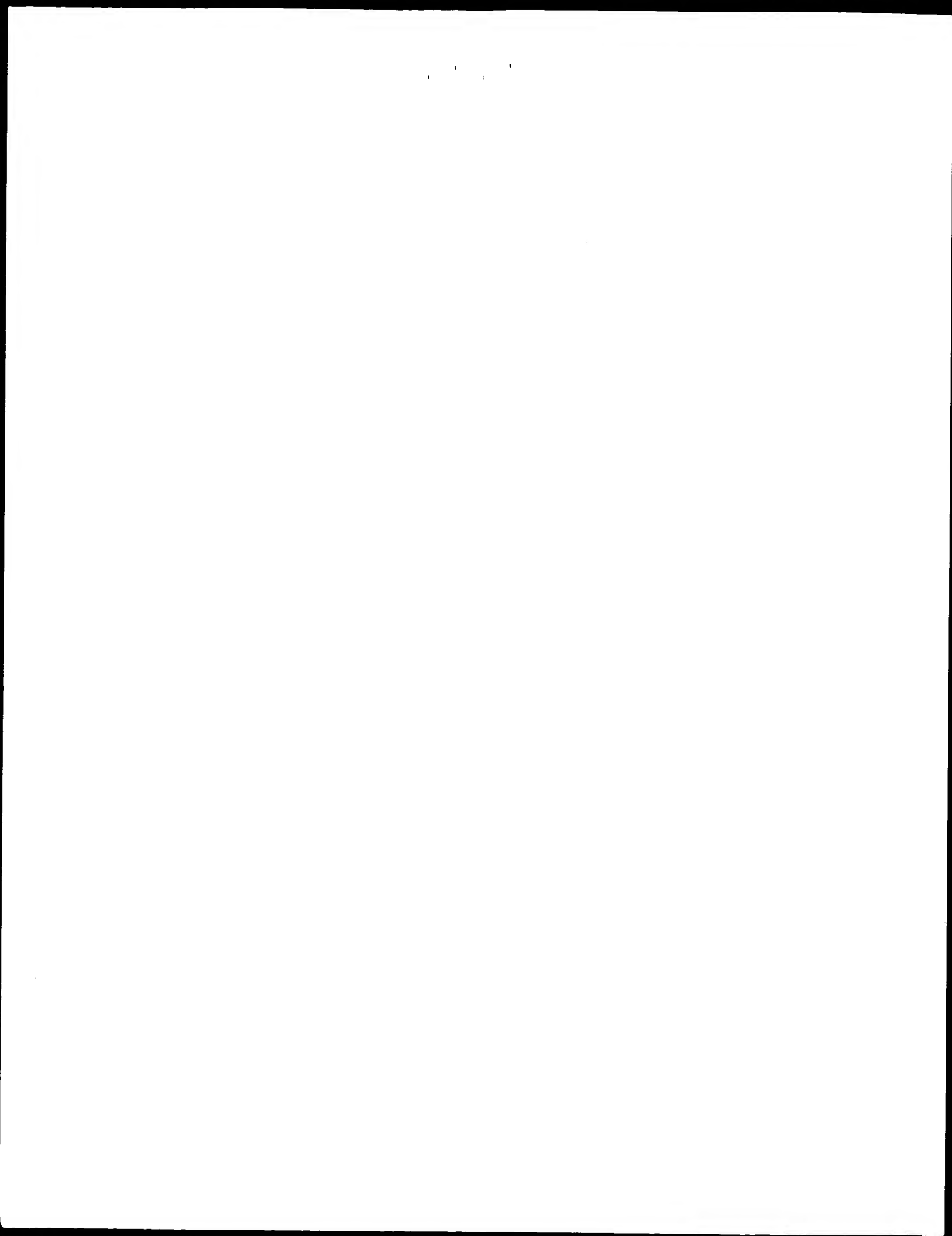
**R1** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfonyl, sulfinyl, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfonyl, -CH<sub>2</sub>-sulfinyl, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, -CH<sub>2</sub>-isoxazol and higher analogues thereof;

**R2** can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea ;

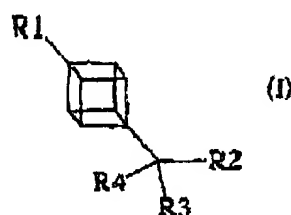
**R3** can be H, aliphatic, aromatic or heterocyclic;

**R4** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfonyl, sulfinyl, borono, tetrazol, isoxazol;

and pharmaceutically acceptable salts thereof.



In particular compounds wherein the compound of Formula I is selected from the group consisting of:



wherein:

R1 is COOH

R2 is NH<sub>2</sub>

R3 can be H or methyl or xanthyl or thioxanthyl or -CH<sub>2</sub>-xanthyl or -CH<sub>2</sub>-thioxanthyl and

R4 is COOH

While all of the compounds of Formula I are believed to demonstrate activity at the metabotropic glutamate receptors (mGluRs), certain groups of Formula I compounds are more preferred for such use.

As noted above, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic





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acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid

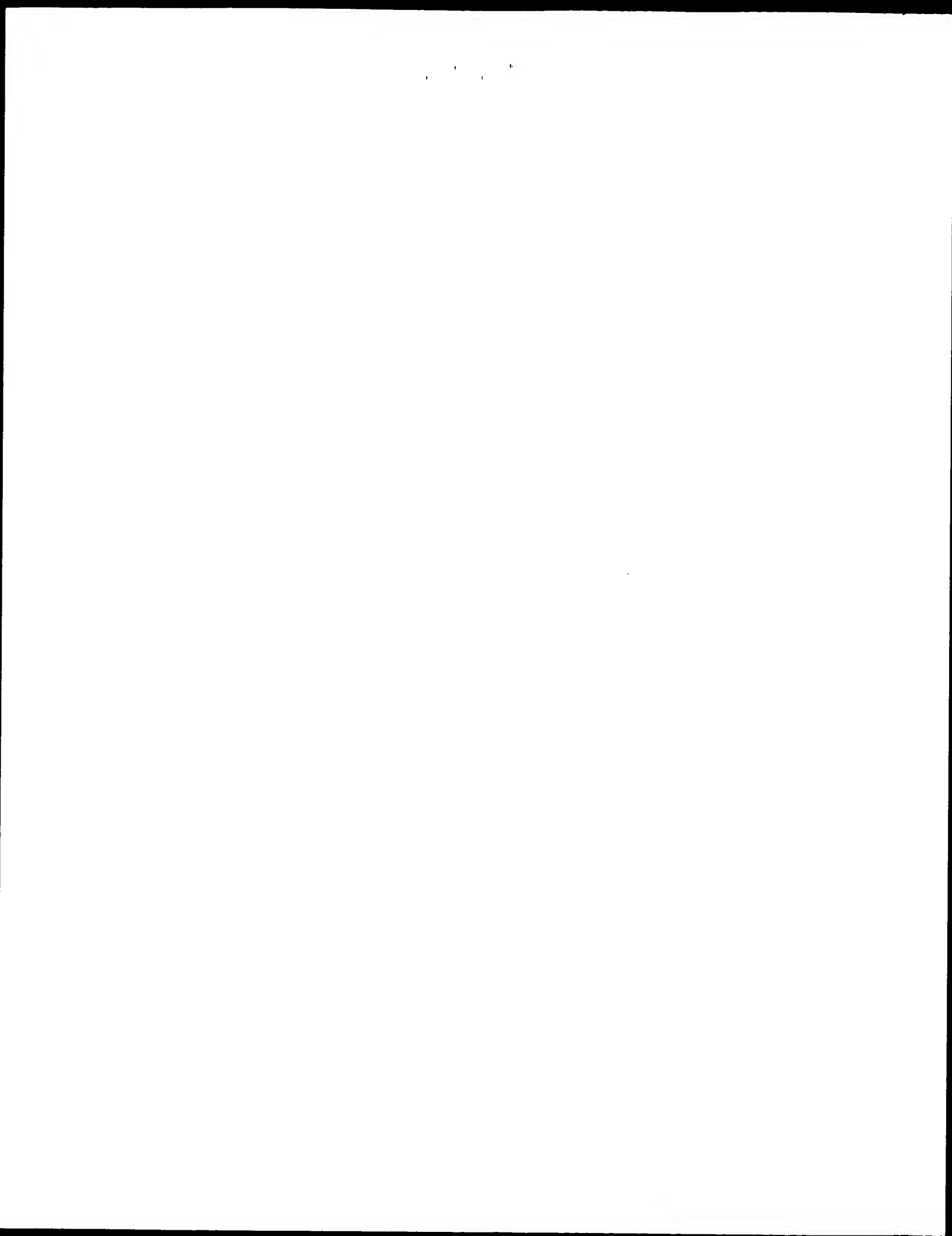
Salts of amine groups may also comprise quarternary ammonium salts in which the amino nitrogen carries a suitable organic group such as an alkyl, alkenyl, alkynyl, or aralkyl moiety.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. This invention further encompasses the pharmaceutically acceptable solvates of the compounds of Formula I. Many of the Formula I compounds can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

The compounds of the present invention have multiple asymmetric (chiral) centers. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of

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diastereomers. All asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

The prefixes "*R*" and "*S*" are used herein as commonly used in organic chemistry to denote the absolute configuration of a chiral center, according to the Cahn-Ingold-Prelog system. The stereochemical descriptor *R* (*rectus*) refers to that configuration of a chiral center with a clockwise relationship of groups tracing the path from highest to second-lowest priorities when viewed from the side opposite to that of the lowest priority group. The stereochemical descriptor *S* (*sinister*) refers to that configuration of a chiral center with a counterclockwise relationship of groups tracing the path from highest to second-lowest priority when viewed from the side opposite to the lowest priority group. The priority of groups is decided using sequence rules as described by Cahn et al., *Angew. Chem.*, 78, 413-447, 1966 and Prelog, V. and Helmchen, G, *Angew. Chem. Int. Ed. Eng.*, 21, 567-583, 1982).

In addition to the *R,S* system used to designate the absolute configuration of a chiral center, the older D-L system is also used in this document to denote relative configuration, especially with reference to amino acids and amino acid derivatives. In this system a Fischer projection of the compound is oriented so that carbon-1 of the parent chain is at the top. The prefix "D" is used to represent the relative configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and "L", that of the isomer in which it is on the left.

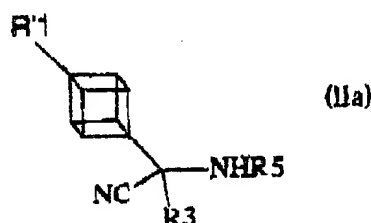
As would be expected, the stereochemistry of the Formula I compounds is critical to their potency as agonists or antagonists. The relative stereochemistry is established early during synthesis, which avoids subsequent stereoisomer separation problems later in the process. Further manipulation of the molecules then employs stereospecific procedures so as to maintain the preferred chirality. The preferred methods of this invention are the methods employing those preferred compounds.

Non-toxic metabolically-labile esters and amides of compounds of Formula I are ester or amide derivatives of compounds of Formula I that are hydrolyzed *in vivo* to afford said compounds of Formula I and a pharmaceutically acceptable alcohol or amine. Examples of metabolically-labile esters include esters formed with (1-6C) alkanols in which the alkanol moiety may be optionally substituted by a (1-8C) alkoxy group, for example methanol, ethanol, propanol and methoxyethanol. Examples of metabolically-labile amides include amides formed with amines such as methylamine



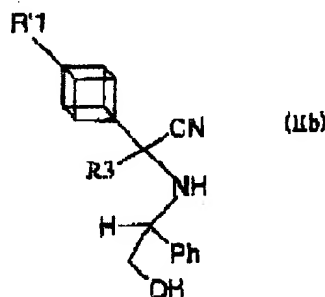
According to another aspect, the present invention provides a process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolyzing a compound of formula (IIa):



wherein: R'1 is an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfonyl, sulfinyl, boronyl, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfonyl, -CH<sub>2</sub>-sulfinyl, -CH<sub>2</sub>-boronyl, -CH<sub>2</sub>-tetrazol, -CH<sub>2</sub>-isoxazol and higher analogues thereof, or a protected form thereof, R3 can be H, aliphatic, aromatic or heterocyclic and R5 represents a hydrogen atom or an acyl group. Preferred values for R5 are hydrogen and (2-6C) alkanoyl groups, such as acetyl; or

(b) deprotecting and hydrolyzing a compound of formula (IIb)



wherein: R'1 and R3 are as defined above; or

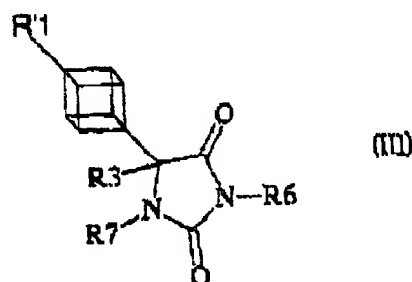


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(c) hydrolyzing a compound of formula:



wherein: R'1 and R3 has the meaning defined above, R6 and R7 each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof; or



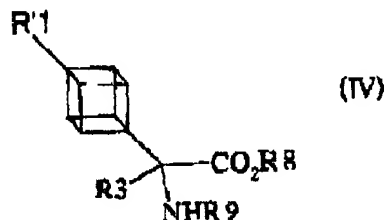


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(d) deprotecting a compound of formula:



wherein:  $R'1$  and  $R3$  has the meaning defined above,  $R8$  represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and  $R9$  represents a hydrogen atom or a nitrogen protecting group;

whereafter, if necessary and/or desired:

- (i) resolving the compound of Formula I;
- (ii) converting the compound of Formula I into a non-toxic metabolically-labile ester or amide thereof;
- and/or;
- (iii) converting the compound of Formula I or a non-toxic metabolically-labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

The protection of carboxylic acid and amino groups is generally described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxyl protecting groups include alkyl groups such as methyl, ethyl, *i*-butyl and *t*-amyl; aralkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and *t*-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine-protecting groups include acyl groups, such as groups of formula  $R9\text{CO}$  in which  $R9$  represents (1-6C) alkyl, (3-10C) cycloalkyl, phenyl(1-6C) alkyl, phenyl(1-6C) alkoxy, or a (3-10C) cycloalkoxy, wherein a phenyl group may optionally be substituted by one or two



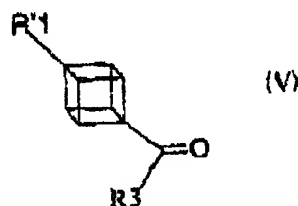
substituents independently selected from amino, hydroxy, nitro, halogeno, (1-6C) alkyl, (1-6C) alkoxy, carboxyl, (1-6C) alkoxycarbonyl, carbamoyl, (1-6C) alkanoylamino, (1-6C) alkylsulphonylamino, phenylsulphonylamino, toluenesulphonylamino, and (1-6C) fluoroalkyl.

The compounds of Formula II are conveniently hydrolyzed in the presence of an acid, such as hydrochloric acid or sulfuric acid, or a base, such as an alkali metal hydroxide, for example sodium hydroxide. The hydrolysis is conveniently performed in an aqueous solvent such as water and at a temperature in the range of 50 to 200 °C.

The compounds of Formula III are conveniently hydrolyzed in the presence of a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline earth metal hydroxide such as barium hydroxide. Suitable reaction media include water. The temperature is conveniently in the range of from 50 to 150 °C.

The compounds of Formula IV may be deprotected by a conventional method. Thus, an alkyl carboxyl protecting group may be removed by hydrolysis. The hydrolysis may conveniently be performed by heating the compound of Formula IV in the presence of either a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline metal hydroxide, such as barium hydroxide, or an acid such as hydrochloric acid. The hydrolysis is conveniently performed at a temperature in the range from 10 to 300 °C. An aralkyl carboxyl protecting group may conveniently be removed by hydrogenolysis. The hydrogenolysis may conveniently be effected by reacting the compound of Formula IV with hydrogen in the presence of a Group VIII metal catalyst, for example a palladium catalyst such as palladium on charcoal. Suitable solvents for the reaction include alcohols such as ethanol. The reaction is conveniently performed at a temperature in the range from 0 to 100 °C. An acyl amine protecting group is also conveniently removed by hydrolysis, for example as described for the removal of an alkyl carboxyl protecting group.

The compounds of Formula II may be prepared by reacting a compound of formula (V):





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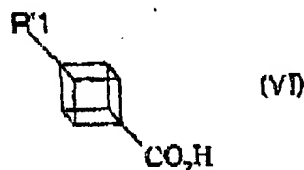
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with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and an ammonium halide, such as ammonium chloride, conveniently in the presence of ultrasound. Thus, the ammonium halide is mixed with chromatography grade alumina in the presence of a suitable diluent such as acetonitrile. The mixture is then irradiated with ultrasound, whereafter the compound of Formula V is added, and the mixture is again irradiated. The alkali metal cyanide is then added, followed by further irradiation with ultrasound.

Individual isomers of compounds of Formula I may be made by reacting a compound of the Formula V with the stereoisomers of the chiral agent (S)- and (R)-phenylglycinol and a reactive cyanide such as trimethylsilyl cyanide.

The compounds of Formula III may be prepared by reacting a compound of Formula V with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and ammonium carbonate or ammonium carbamate. Convenient solvents include water, dilute ammonium hydroxide, alcohols such as methanol, aqueous methanol and aqueous ethanol. Conveniently the reaction is performed at a temperature in the range of from 10 to 150 °C. If desired, the compounds of Formula III may then be alkylated, for example using an appropriate compound of formula R6 Cl and/or R7 Cl.

The compounds of Formula V can be prepared by reacting a compound of formula:



with a chlorinating agent such as thionyl chloride or phosphorous (V) chloride, followed by reaction with organo copper or organo metal or Grignard reagent derived from R3 X or by reaction with ethyl hydrogen malonate in the presence of organolithium, wherein R3 has the meaning defined above and X is halogen.

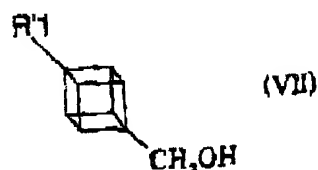
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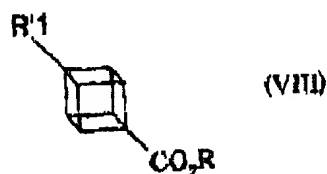
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The compounds of Formula V can also be prepared by oxidizing a compound of formula



under Swern conditions.

The compounds of Formula VI can be prepared from compounds of formula:



by reduction.

When R'1 is CO<sub>2</sub>Me, this compound can be bought commercially. When R'1 is another substituent, the compound of Formula VIII can be made using standard procedures.

Many of the intermediates described herein, for example the compounds of Formula II, III and IV are believed to be novel, and are provided as further aspects of the invention.

The Formula I compounds of the present invention are agonists or antagonists at certain metabotropic excitatory amino acid receptors (mGluRs). Therefore, another aspect of the present invention is a method of affecting mGluRs in mammals, which comprises administering to a mammal requiring modulated excitatory amino acid neurotransmission a pharmacologically-effective amount of a compound of Formula I. The term "pharmacologically-effective amount" is used to represent an amount of the compound of the invention that is capable of affecting the mGluRs. By affecting, a compound of the invention is acting as an agonist or antagonist. When a compound of the





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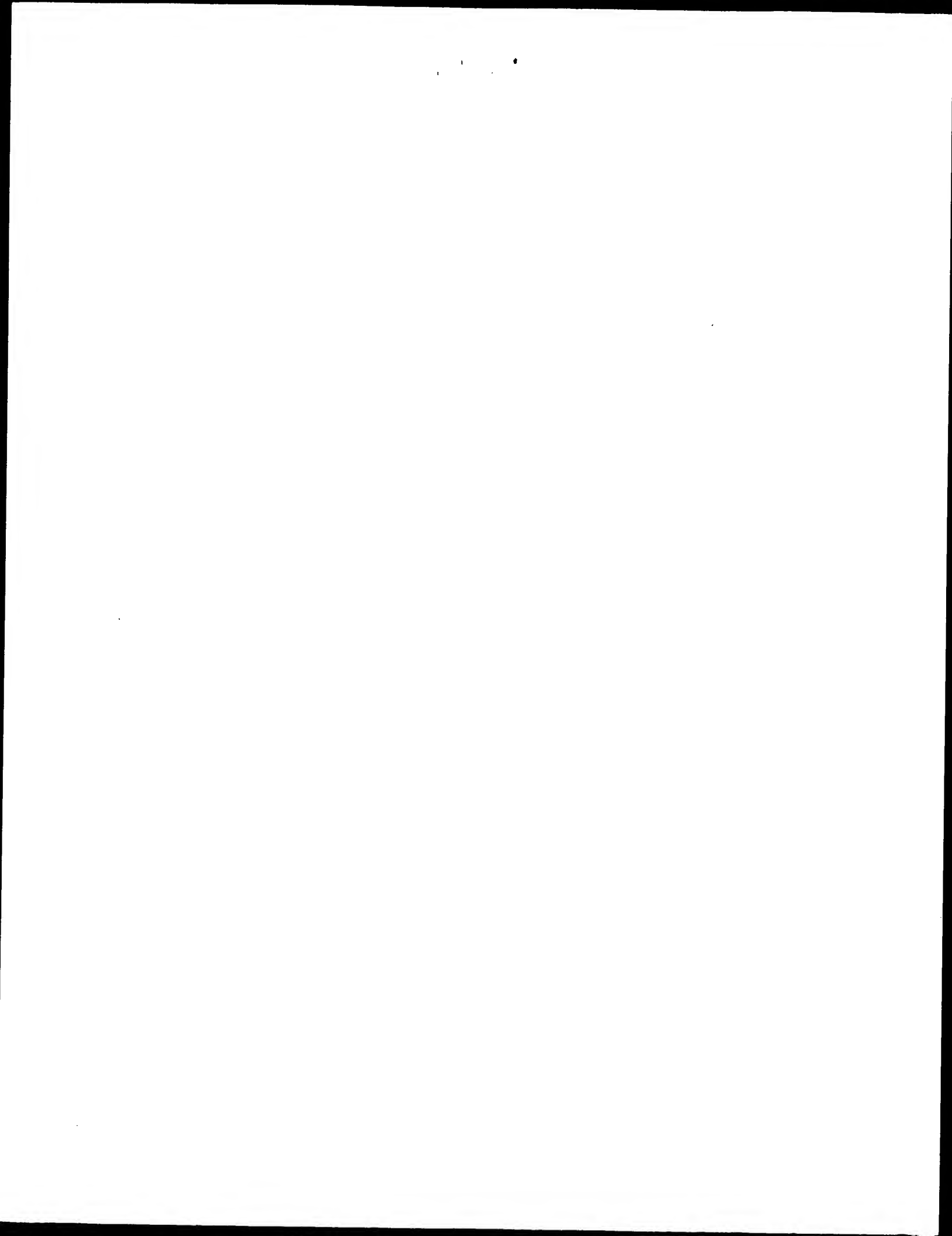
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invention acts as an agonist, the interaction of the compound with the excitatory amino acid receptor mimics the response of the interaction of this receptor with its natural ligand (i.e. L-Glutamic acid). When a compound of the invention acts as an antagonist, the interaction of the compound with the excitatory amino acid receptor blocks the response of the interaction of this receptor with its natural ligand (i.e. L-Glutamic acid).

The particular dose of compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the compound may be administered by continuous infusion. A typical daily dose will contain from about 0.001 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 20 mg/kg.

A variety of physiological functions have been shown to be subject to influence by excessive or inappropriate stimulation of excitatory amino acid transmission. The Formula I compounds of the present invention are believed (through their interactions at the mGluRs) to have the ability to treat a variety of neurological disorders in mammals associated with this condition, including acute neurological disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia (e.g. stroke and cardiac arrest), spinal cord trauma, head trauma, perinatal hypoxia, and hypoglycemic neuronal damage. The Formula I compounds are believed to have the ability to treat a variety of chronic neurological disorders, such as Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage and retinopathy, cognitive disorders, and idiopathic and drug-induced Parkinson's disease. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of Formula I.

The Formula I compounds of the present invention (through their interactions at the mGluRs) are also believed to have the ability to treat a variety of other neurological disorders in mammals that are associated with glutamate dysfunction, including muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, anxiety and related disorders (e.g. panic attack), emesis, brain edema, chronic pain, sleep disorders, Tourette's syndrome, attention



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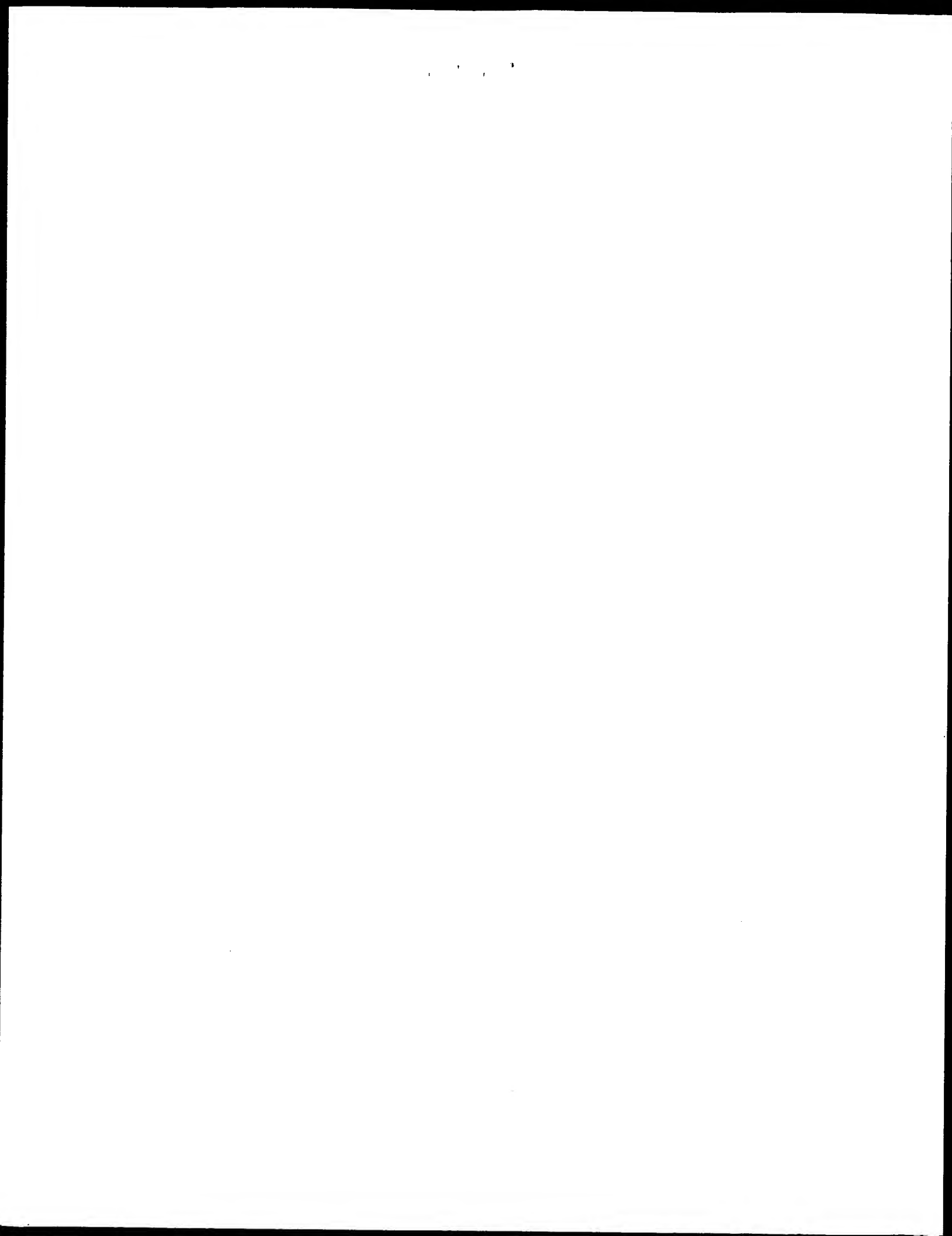
deficit disorder, and tardive dyskinesia. Therefore, the present invention also provides methods for treating these disorders which comprise administering to a patient in need thereof an effective amount of the compound of Formula I.

The Formula I compounds of the present invention (through their interactions at the mGluRs) are also believed to have the ability to treat a variety of psychiatric disorders, such as schizophrenia, anxiety and related disorders (e.g. panic attack), depression, bipolar disorders, psychosis, and obsessive compulsive disorders. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of Formula I.

The pharmacological properties of the compounds of the invention can be illustrated by determining their effects in various functional in vitro assays. The compounds of the invention were studied in an in vitro assay that measured the inhibition of PI hydrolysis or the formation of cyclic AMP in Chinese hamster ovary cell lines expressing mGluR<sub>1a</sub>, mGluR<sub>2</sub> and mGluR<sub>4</sub>, cloned metabotropic glutamate receptors.

### Principle

So far eight different clones of the G-protein-coupled mGluRs have been identified (Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426). These receptors function to modulate the presynaptic release of L-Glutamate, and the postsynaptic sensitivity of the neuronal cell to L-Glutamate excitation. Based on pharmacology, sequence homology and the signal transduction pathway that they activate, the mGluRs have been subclassified into three groups. The mGluR<sub>1</sub> and mGluR<sub>5</sub> receptors form group I. They are coupled to hydrolysis of phosphatidylinositol (PI) and are selectively activated by (RS)-3,5-dihydroxyphenylglycine (Brabet et al., *Neuropharmacology*, 34, 895-903, 1995). Group II comprises mGluR<sub>2</sub> and mGluR<sub>3</sub> receptors. They are negatively coupled to adenylate cyclase and are selectively activated by (2S,1'R,2R,3'R)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV; Hayashi et al., *Nature*, 366, 687-690, 1993). Finally, the mGluR<sub>4</sub>, mGluR<sub>6</sub>, mGluR<sub>7</sub> and mGluR<sub>8</sub> receptors belong to group III. They are also negatively coupled to adenylate cyclase and are selectively activated by (S)-2-amino-4-phosphonylbutyric acid (L-AP4; Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426).



### Cell Culture

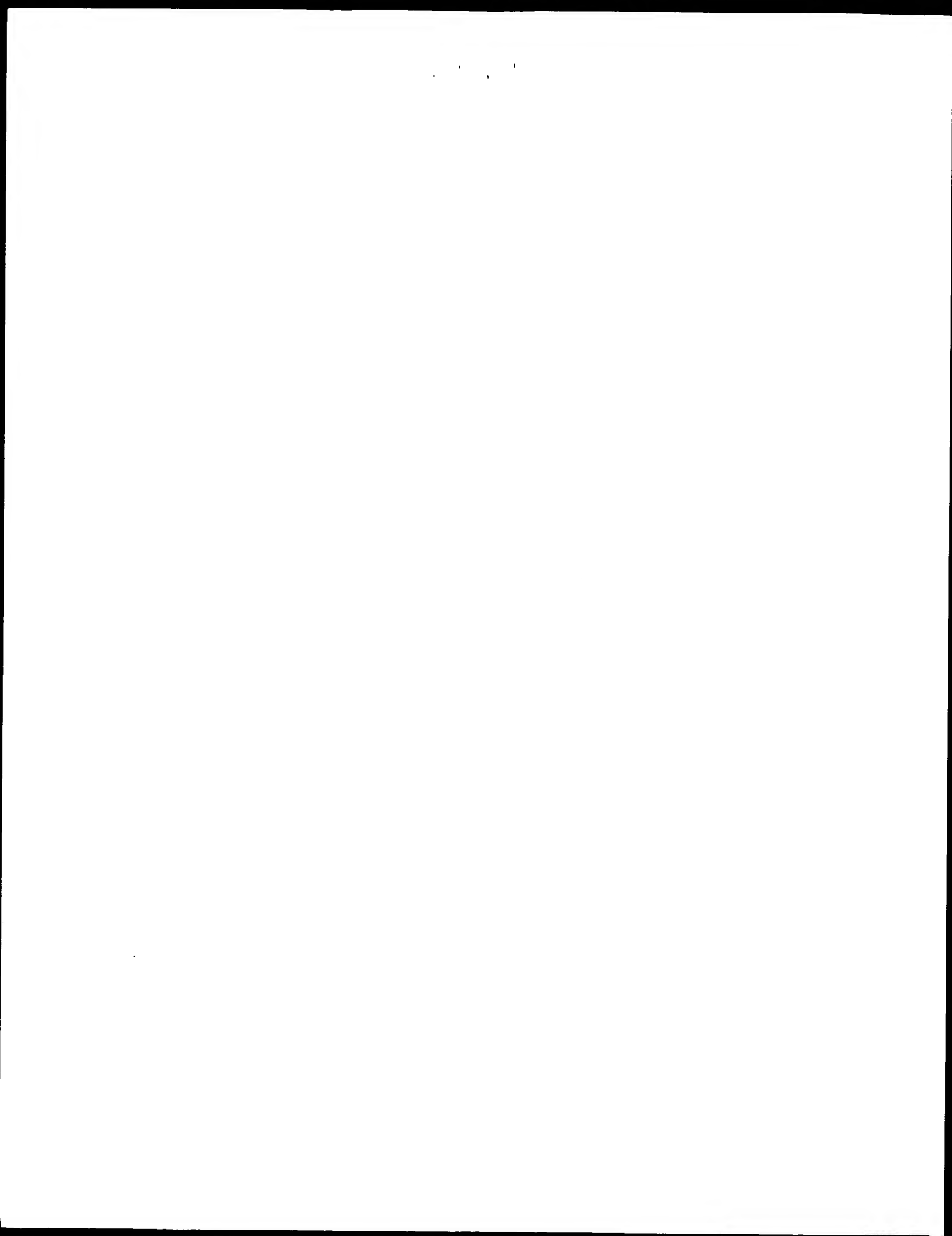
The Chinese hamster ovary cell lines expressing mGluR<sub>1a</sub>, mGluR<sub>2</sub> and mGluR<sub>4a</sub> receptors have been described previously (Aramori and Nakanishi, *Neuron* 8, 757-765; 1992; Tanabe et al., *Neuron* 8, 169-179, 1992; Tanabe et al., *J. Neurosci.* 13, 1372-1378). They were maintained at 37°C in a humidified 5% CO<sub>2</sub> incubator in Dulbecco's Modified Eagle Medium (DMEM) containing a reduced concentration of (S)-glutamine (2mM) and were supplemented with 1% proline, penicillin (100 U/ml), streptomycin (100 mg/ml) and 10% dialyzed fetal calf serum (all GIBCO, Paisley). Two days before assay  $1.8 \times 10^6$  cells were divided into the wells of 24 well plates.

### Second Messenger Assays

PI hydrolysis was measured as described previously (Hayashi et al., *Br. J. Pharmacol.* 107, 539-543, 1992; Hayashi et al., *J. Neurosci.* 14, 3370-3377, 1994). Briefly, the cells were labeled with [<sup>3</sup>H]inositol (2 µCi/ml) 24 h prior to the assay. For agonist assays, the cells were incubated with ligand dissolved in phosphate-buffered saline (PBS)-LiCl for 20 min, and agonist activity was determined by measurement of the level of <sup>3</sup>H-labeled mono-, bis- and tris-inositol phosphates by ion-exchange chromatography. For antagonist assays, the cells were preincubated with the ligand dissolved in PBS-LiCl for 20 min prior to incubation with ligand and 10 µM (L)-Glutamic acid for 20 min. The antagonist activity was then determined as the inhibitory effect of the (L)-Glutamic acid-mediated response. The assay of cyclic AMP formation was performed as described previously (Hayashi et al., *Br. J. Pharmacol.* 107, 539-543, 1992; Hayashi et al., *J. Neurosci.* 14, 3370-3377, 1994). Briefly, the cells were incubated for 10 min in PBS containing the ligand and 10 µM forskolin and 1mM 3-Isobutyl-1-methylxanthine (IBMX; both Sigma, St. Louis, MO, USA). The agonist activity was then determined as the inhibitory effect of the forskolin-induced cyclic AMP formation. For antagonist assay, the cells were preincubated with ligand dissolved in PBS containing 1 mM IBMX for 20 min prior to a 10 min incubation in PBS containing the ligand, 20 µM (mGluR<sub>2</sub>) or 50 µM (mGluR<sub>4a</sub>), (L)-Glutamic acid, 10 µM Forskolin and 1 mM IBMX.

### Results

Some of the compounds of the invention were tested for antagonist activity against Chinese hamster



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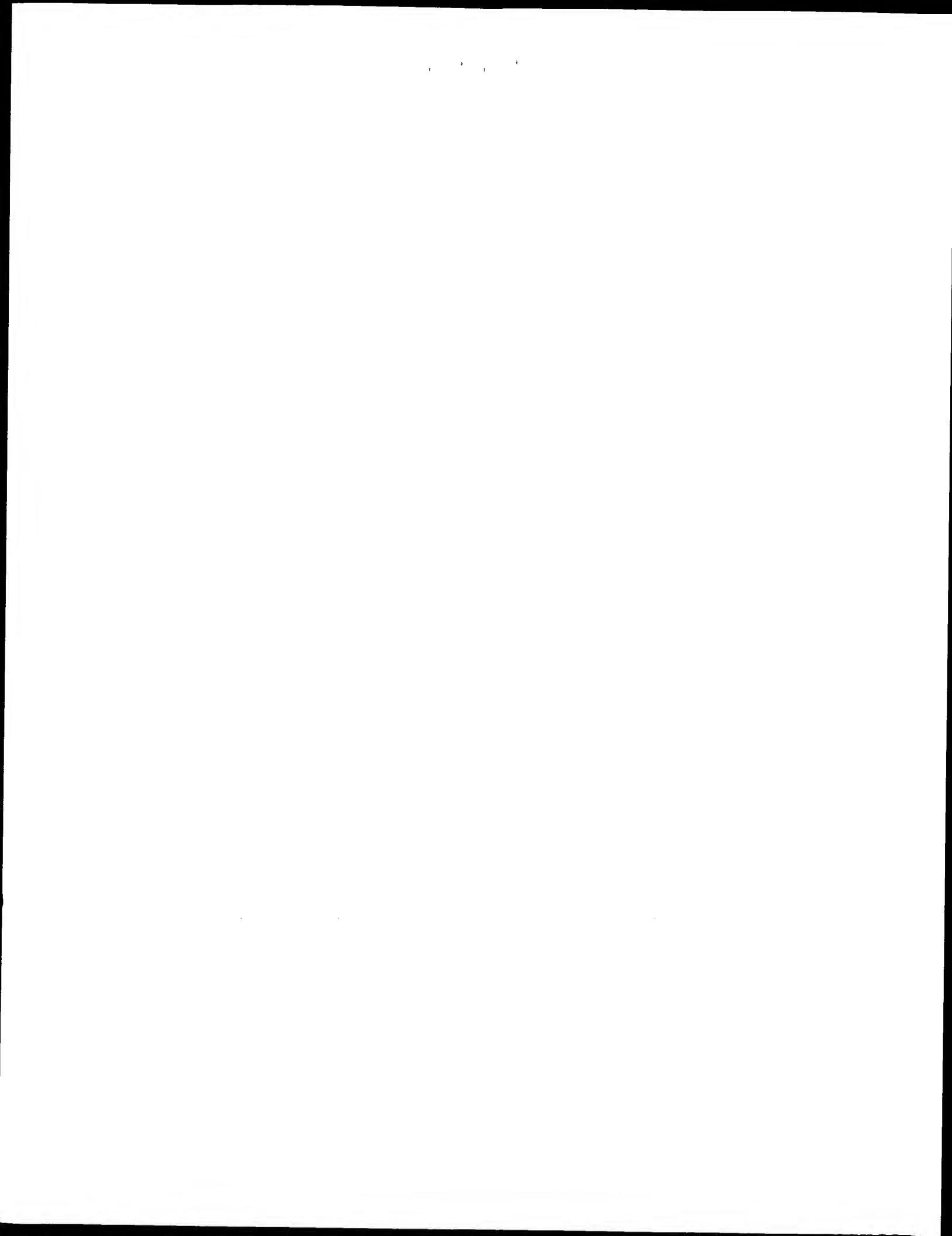
ovary cell lines expressing mGluR<sub>1α</sub>, mGluR<sub>2</sub> and mGluR<sub>4</sub>, cloned mGluRs at a concentration of 1 mM. When tested as antagonists of the increase in PI hydrolysis evoked by 10 μM (L)-Glutamic acid, some compounds of the invention effectively blocked this increase in PI hydrolysis by an action at the mGluR<sub>1α</sub> receptor. The data for one of the compounds of the invention is shown in Figure 1 below.

According to another aspect, the present invention provides a method of modulating one or more metabotropic glutamate receptor functions in a warm-blooded mammal which comprises administering an effective amount of a compound of Formula I, or a non-toxic metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof.

The compounds of the present invention are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical formulation comprising a compound of Formula I and a pharmaceutically-acceptable carrier, diluent, or excipient. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active ingredient.

The compounds of Formula I are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

The present invention also provides pharmaceutical compositions containing compounds as disclosed in the claims in combination with one or more pharmaceutically acceptable, inert or physiologically active, diluent or adjuvant. The compounds of the invention can be freeze-dried and, if desired, combined with other pharmaceutically acceptable excipients to prepare formulations for administration. These compositions may be presented in any form appropriate for the administration route envisaged. The parenteral and the intravenous route are the preferential routes for administration.





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Compounds of the general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium



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carboxymethylcellulose, methyl cellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia: dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example hepta-decaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl-*p*-hydroxy benzoate, one or more colouring agents, one or more flavouring agents or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example peanut oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin.

The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or peanut oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents



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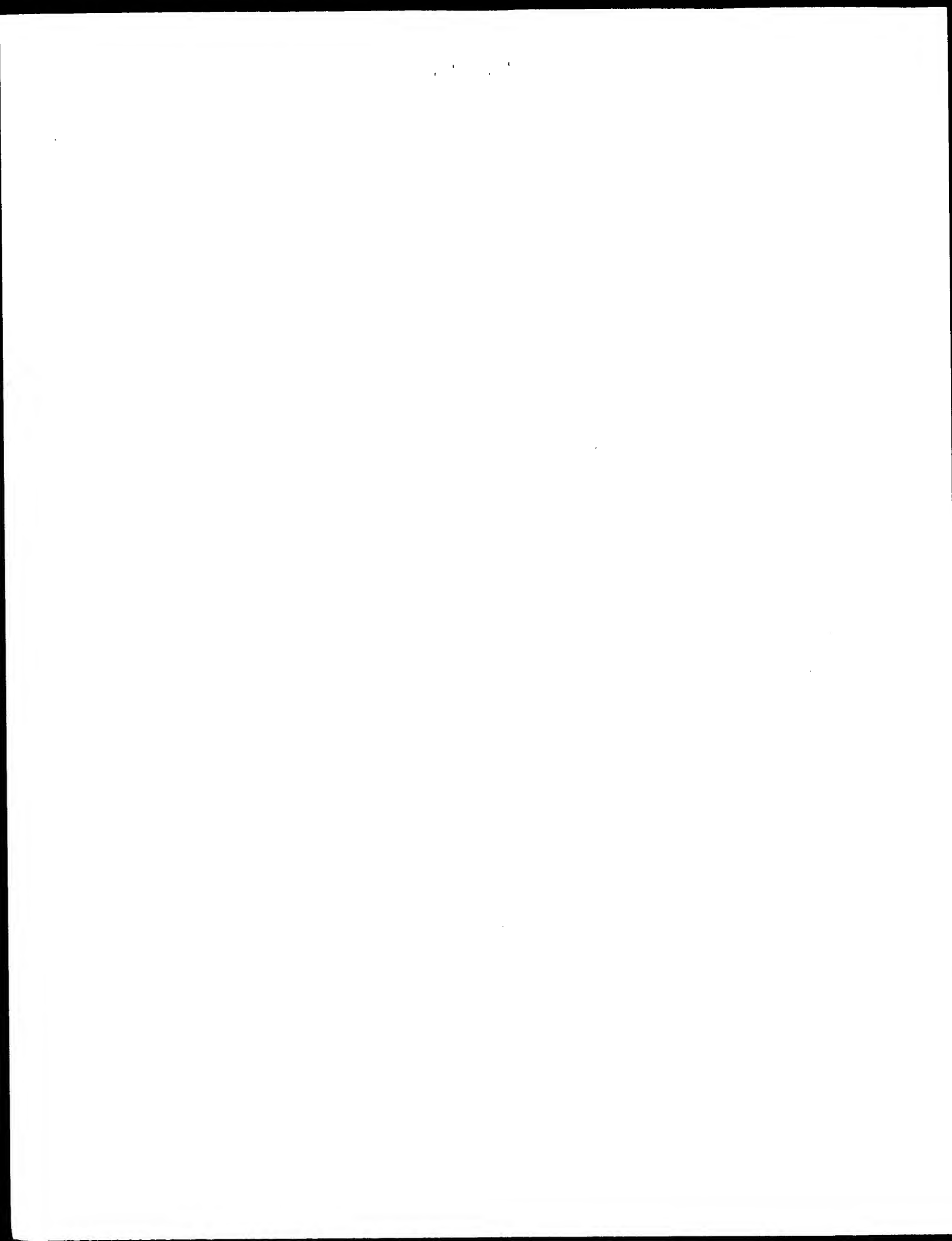
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Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or a suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compound(s) of the general Formula I may be administered, together or separately, in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compound(s) of general Formula I may be administered, together or separately, parenterally in sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

The dosage to be administered is not subject to defined limits, but it will usually be an effective amount. It will usually be the equivalent, on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active free drug to achieve its desired pharmacological and physiological effects. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.



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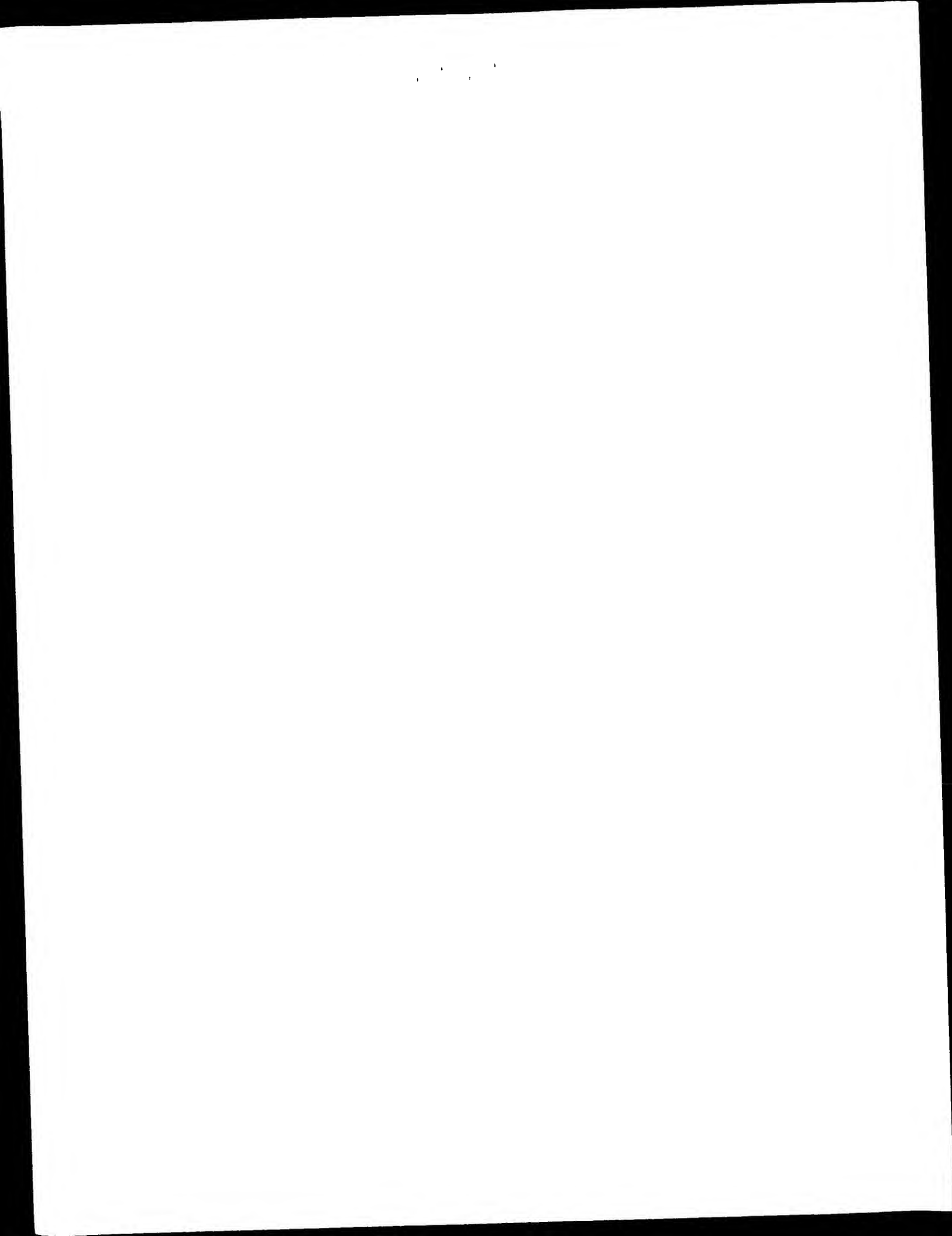
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The active compound is effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.01 to about 30 mg/kg of body weight. A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 mg to about 500 mg, more preferably about 25 mg to about 300 mg of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.





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**Formulation 1**

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities

**Formulation 2**

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665

The components are blended and compressed to form tablets each weighing 665 mg.

**Formulation 3**

An aerosol solution is prepared containing the following components:



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	Weight %
Active Ingredient	0.25
Ethanol	29.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	100

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30 °C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

#### Formulation 4

Tablets each containing 60 mg of active ingredient are made as follows:

	Quantity (mg/tablet)
Active Ingredient	60
Starch	45
Microcrystalline cellulose	35
Polyvinylpyrrolidone	4
Sodium carboxymethyl starch	4.5
Magnesium stearate	0.5
Talc	1.0
Total	150

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders that are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed

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through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

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**Formulation 5**

Capsules each containing 80 mg medicament are made as follows:

	Quantity (mg/capsule)
Active Ingredient	80
Starch	59
Microcrystalline cellulose	59
Magnesium stearate	2
Total	200

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 sieve, and filled into hard gelatin capsules in 200 mg quantities.

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**Formulation 6**

Suppositories each containing 225 mg of active ingredient may be made as follows:

	Quantity (mg/suppository)
Active Ingredient	225
Saturated fatty acid glycerides	2000
Total	2225

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.



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*Formulation 7*

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

Active Ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mL
Benzoic acid solution	0.10 mL
Flavour	q.v.
Color	q.v.
Purified water to total	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

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*Formulation 8*

An intravenous formulation may be prepared as follows:

	Quantity
Active Ingredient	100 mg
Mannitol	100 mg
5 N Sodium hydroxide	200 mL
Purified water to total	5 mL

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*Formulation 9*

A topical formulation may be prepared as follows:





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	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White soft paraffin to	100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

### Formulation 10

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

	Quantity (mg/tablet)
Active Ingredient	10.0
Glycerol	210.5
Water	143.0
Sodium Citrate	4.5
Polyvinyl Alcohol	26.5
Polyvinylpyrrolidone	15.5
Total	410.0

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90 °C. When the polymers have gone into solution, the solution is cooled to about 50°-55 °C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size



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Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts.

The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, for example, U.S. Pat. No. 5,023,252, issued Jun. 11, 1991) herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Pat. No. 5,011,472, issued Apr. 30, 1991, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions that can transiently open the blood-brain barrier.

### EXAMPLES

The following Examples illustrate the invention. The following abbreviations are used in the Examples: EtOAc, ethyl acetate; THF, tetrahydrofuran; EtOH, ethanol; TLC, thin layer chromatography; GC, gas chromatography; HPLC, high pressure liquid chromatography; m-CPBA, m-chloroperbenzoic acid; Et<sub>2</sub>O, diethyl ether; DMSO, dimethyl sulfoxide; DBU, 1,8-diazabicyclo-[5.4.0]undec-7-ene; MTBE, methyl *t*-butyl ether; FDMS, field desorption mass spectrometry and *rt*, room temperature.



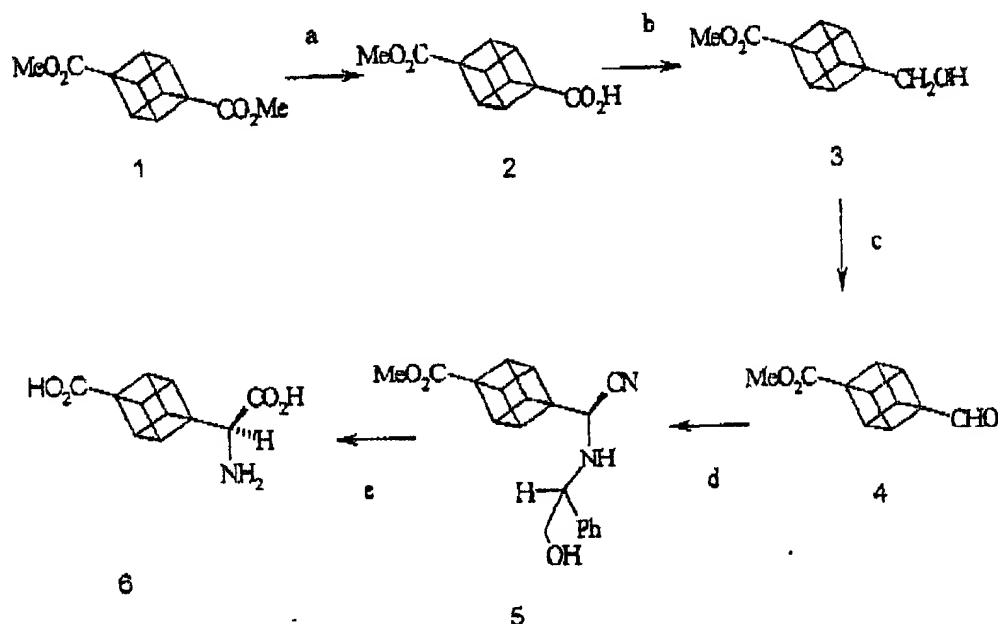
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## Example 1: Synthesis of Cubanylglycinates IGT 1.0 series



## Preparation 1: 4-methoxycarbonylcubane carboxylic acid

A solution of cubane dimethyl ester (6.0g, 27.24 mmol) in 182 mL of dry THF is stirred under  $N_2$  at room temperature. A solution of methanolic NaOH (26.7 mmol, 10.7 mL 2.5 M) is added dropwise from a pressure equalized addition funnel and the resulting solution stirred at room temperature for 16 h. The mixture is evaporated under reduced pressure at r.t., the residue is taken up in 66 mL of water and extracted with 3 x 25 mL of chloroform. The aqueous layer is acidified to pH 3 with concentrated HCl and extracted with 3 x 30 mL of chloroform. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give (2) 182-183 °C:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.72 (s, 3H), 4.27 (m, 6H).  
Yield 5.1 g (91%).

## Preparation 2: 4-methoxycarbonyl-1-(hydroxymethyl) cubane

The mono acid (2) (0.48 g) is dissolved in dry THF (5 mL) and cooled to -70 °C. A solution of  $BH_3$  in THF is added slowly with stirring. The reaction mixture is stirred at -78 °C for 4 hrs and



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allowed to come to room temperature. Water (3 mL) is added and stirred for 30 min, potassium carbonate (0.85 g) is added and the solution extracted with Et<sub>2</sub>O. The organic phase is dried over magnesium sulfate and evaporated to give the alcohol (3) 0.46 g (100%) m.p. 83-85 °C. <sup>1</sup>H NMR (200 MHz, solvent) δ: 1.58 (s, 1H), 3.62 (s, 3H), 3.72 (s, 2H), 3.81 (m, 3H), 4.1 (m, 3H).

*Preparation 3: 4-methoxycarbonyl-1-(formyl) cubane*

DMSO (0.7 mL, 9.68 mmol) is added to oxalyl chloride (0.42 mL, 4.84 mmol) in 12 mL of CH<sub>2</sub>Cl<sub>2</sub> at -78 °C. The alcohol (3) (0.46 g, 2.42 mmol) in 3 mL CH<sub>2</sub>Cl<sub>2</sub> is added and stirred at -78 °C for 1.5 h. Triethylamine (2.0 mL, 14.4 mmol) is added and the mixture is allowed to come to 0 °C. Saturated ammonium chloride solution is added and the phases separated, the aqueous layer is extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers are dried (MgSO<sub>4</sub>), then evaporated to give crude product which is purified by flash chromatography (1:1 hexanes:diethyl ether) to give 0.35 g (76%) of pure product (4). <sup>1</sup>H NMR (200 MHz, solvent) δ: 3.7 (s, 3H), 4.2 (m, 3H), 4.32 (m, 3H), 9.72 (s, 1H).

*Preparation 4: 4-methoxycarbonyl-1-(2'-hydroxy-1'-phenylethyl) methylnitrilucubane*

(R)-phenylglycinol (257 mg, 1.87 mmol) is added to a solution of the aldehyde (4) (0.35 g, 1.84 mmol) in 14 mL of methanol. The solution is cooled to 0 °C and TMSCN (0.49 mL, 3.68 mmol) is added and the mixture stirred at 0 °C overnight. Evaporation of the solvent leaves a residue which is purified by chromatography (diethyl ether:hexanes, 3:1) to give 0.48 g (77%) of pure product (5). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.23 (s, 1H), 2.6 (br, 1H), 3.5-3.75 (m, 2H), 3.7 (s, 3H), 3.9 (m, 3H), 4.11 (dd, 1H), 4.2 (m, 3H), 7.3 (s, 5H).

*Preparation 5: 4-carboxy-1-cubanylglycine*

Lead acetate (0.69 g, 1.57 mmol) is added to a stirred solution of nitrile (5) (0.48 g, 1.42 mmol) in dry methanol/dichloromethane 1:1 (12 mL). After 10 min 10 mL of water is added and the suspension filtered through celite. The organic layer is dried and evaporated to give the crude imine. The crude imine is refluxed with 6N HCl (30 mL) for 6 hr. The solution is evaporated to dryness and placed on anion exchange resin, eluting with 1N acetic acid to yield the product (6). mp. 241 °C (dec.) <sup>1</sup>H NMR (D<sub>2</sub>O) δ: 3.96 (s, 1H), 4.01 (m, 3H), 4.14 (m, 3H).





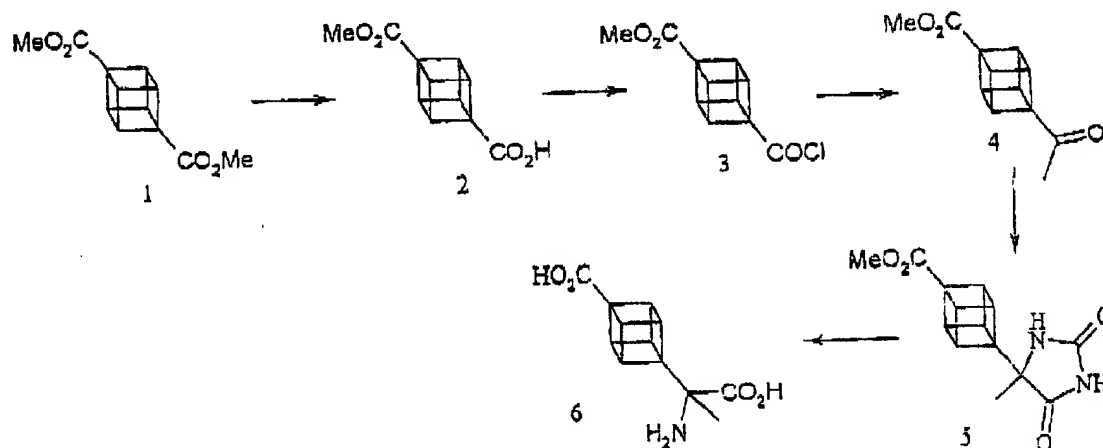
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## Example 2

*Preparation 1: 4-methoxycarbonylcubane carboxylic acid*

A solution of cubane dimethyl ester (6.0g, 27.24 mmol) in 182 mL of dry THF is stirred under  $N_2$  at r.t. a solution of methanolic NaOH (26.7 mmol, 10.7 mL 2.5 M) is added dropwise from a pressure equalized addition funnel and the resulting solution stirred at r.t. for 16 h. The mixture is evaporated under reduced pressure at r.t., the residue is taken up in 66 mL of water and extracted with 3 x 25 mL of chloroform. The aqueous layer is acidified to pH 3 with concentrated HCl and extracted with 3 x 30 mL of chloroform. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give (2) 182-183 °C:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.72 (s, 3H), 4.27 (m, 6H). Yield 5.1 g (91%).

*Preparation 2: 4-methoxycarbonylcubane-1-carbonyl chloride*

The monomethyl ester (2) (1.37 g, 6.65 mmol) is dissolved in 15 mL of thionyl chloride and gently refluxed overnight. The thionyl chloride is evaporated off and the resultant residue containing (3) was used immediately without further purification.

The first part of the paper discusses the importance of maintaining accurate records of all transactions. It is essential for the business to have a clear and concise record of all income and expenses. This will help in the preparation of the tax return and in the event of an audit. The second part of the paper discusses the importance of keeping up to date with the latest tax laws and regulations. It is essential for the business to have a clear understanding of the current tax environment in order to make the most of the available deductions and credits. The third part of the paper discusses the importance of having a good relationship with the tax authorities. It is essential for the business to have a clear understanding of the requirements of the tax authorities and to be able to communicate effectively with them. The fourth part of the paper discusses the importance of having a good understanding of the business's financial position. It is essential for the business to have a clear understanding of its income and expenses in order to make the most of the available deductions and credits. The fifth part of the paper discusses the importance of having a good understanding of the business's tax obligations. It is essential for the business to have a clear understanding of the requirements of the tax authorities in order to avoid any penalties or interest. The sixth part of the paper discusses the importance of having a good understanding of the business's tax credits. It is essential for the business to have a clear understanding of the requirements of the tax authorities in order to make the most of the available credits. The seventh part of the paper discusses the importance of having a good understanding of the business's tax deductions. It is essential for the business to have a clear understanding of the requirements of the tax authorities in order to make the most of the available deductions. The eighth part of the paper discusses the importance of having a good understanding of the business's tax liabilities. It is essential for the business to have a clear understanding of the requirements of the tax authorities in order to avoid any penalties or interest. The ninth part of the paper discusses the importance of having a good understanding of the business's tax returns. It is essential for the business to have a clear understanding of the requirements of the tax authorities in order to avoid any penalties or interest. The tenth part of the paper discusses the importance of having a good understanding of the business's tax records. It is essential for the business to have a clear understanding of the requirements of the tax authorities in order to avoid any penalties or interest.

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*Preparation 3: 4-methoxycarbonylcubane-1-methyl ketone*

A suspension of copper iodide (1.49 g, 7.83 mmol) in 30 mL of dry THF is stirred at 0°C. Methyl lithium (15.75 mmol, 11.2 mL of 1.4 M) was added and stirred at 0°C for 30 min, then cooled to

-78°C. A solution of 1.6 g, 7.12 mmol of (3) in 10 mL dry THF is added and the resultant mixture stirred for 1 h. at -78°C. The mixture was quenched with saturated ammonium chloride solution (15 mL) and extracted with 3 x 30 mL of diethyl ether. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give crude (4). The product was purified by silica chromatography (hexanes:ethyl acetate, 2:1) to give 1.0 g of product (yield 69%), m.p. 87-89°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.17 (s, 3H), 3.7 (s, 3H), 4.21 (m, 6H).

*Preparation 4: 4-methoxycarbonylcubane-1-methyl-1-(5,5'-hydantoin)*

A solution of the methyl ketone (4) (1.0 g, 4.9 mmol) in 40 mL of ethanol and 5.8 mL of 1 N NaOH, is stirred at 70°C for 4 h. The resulting solution is evaporated to dryness under reduced pressure and redissolved in 1:1 ethanol: water (20 mL). To this solution is added potassium cyanide (0.35 g, 5.4 mmol) and ammonium carbonate (0.96 g, 9.8 mmol) and the mixture heated in a sealed tube at 85°C for 24 h. The reaction is cooled, acidified with 6 N HCl and reduced in volume until a precipitate forms. The precipitate is filtered and the filtrate evaporated to dryness and extracted with ethyl acetate. The solvent is evaporated and the product combined with the residue from above to give (5) as a white solid. Yield 0.95 g (75%) m.p. 244-248°C. NMR <sup>1</sup>H (DMSO) δ 1.18 (s, 3H), 3.9 (m, 3H), 4.0 (m, 3H), 8.1 (s, 1H), 10.6 (s, 1H).

*Preparation 5: 4-carboxycubane-1-methylglycine*

The hydantoin (5) (0.95 g, 3.65 mmol) is dissolved in 30 mL of 2 N NaOH and heated to 170°C in a sealed tube for 20 h. The reaction is cooled and filtered to remove precipitate and the filter cake washed with 3 x 10 mL of water. The combined aqueous washings are evaporated to give crude (6) which is applied to Spectrum 1X4 anion exchange resin, eluted with 0.5 N acetic acid. Isolation by evaporation and crystallization gives (6) as colorless crystals. m.p. >250°C (decomp) NMR. <sup>1</sup>H (D<sub>2</sub>O) δ 1.38 (s, 3H), 3.95 (s, 6H)



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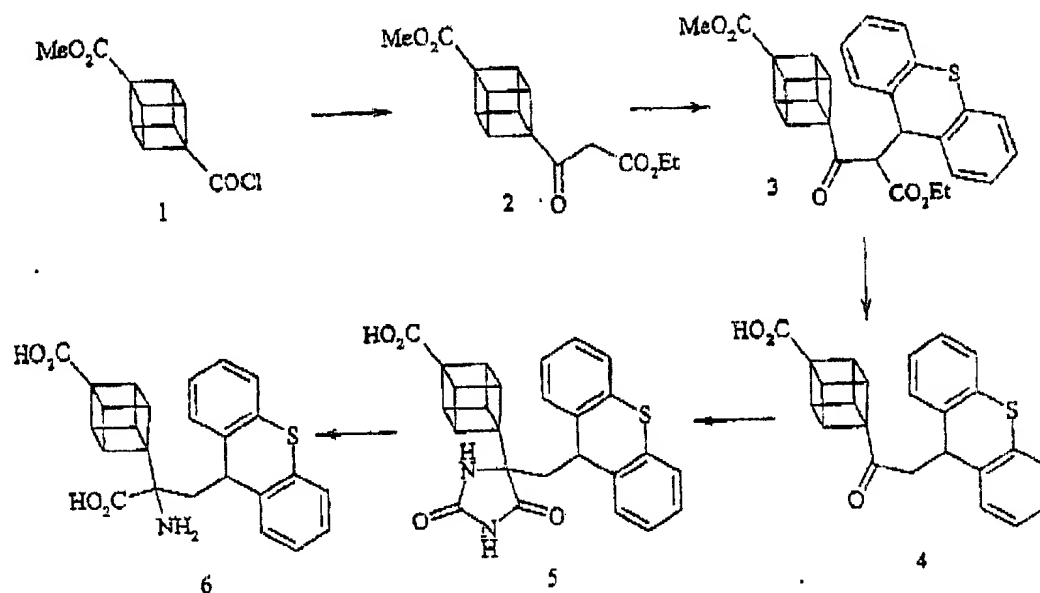
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## Example 3

*Preparation 1: 4-methoxycarbonylcubane-1-acetyl ethylcarboxylate.*

n-butyl lithium (34.83 mmol, 23.5 mL of 1.5 M) is added dropwise to a stirred solution of ethyl hydrogen malonate (2.32 g, 17.41 mmol) in 80 mL of dry THF under  $\text{N}_2$  at  $-78^\circ\text{C}$ . The mixture was warmed to  $-30^\circ\text{C}$  over 0.5 h and then re-cooled to  $-78^\circ\text{C}$ . The acid chloride of cubane monomethyl ester from example (2) above (2.35 g, 10.46 mmol) in 7 mL of THF is added dropwise to the stirred solution. The reaction is warmed slowly to r.t and stirred for a further 1 h. The solution is poured into 50 mL of 1 N HCl and extracted with 3 x 50 mL of diethyl ether. The combined organic extracts are further extracted with 20 mL of saturated sodium hydrogen carbonate and brine, dried over magnesium sulphate, filtered and evaporated to give crude (2). The product is purified by column chromatography on silica with hexanes: ethyl acetate 2:1 to yield 2.5 g (86%) of (2).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.2 (t, 3H) 3.4 (s, 2H), 3.65 (s, 3H), 4.2 (m, 8H).

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*Preparation 2: 4-methoxycarbonylcubane-1-(thioxanthyl)-acetyl ethylcarboxylate.*

cubane- $\beta$ -ketoester (2) (1.15g, 4.16 mmol) and thioxanthene-9-ol (0.88g, 4.1 mmol) are dissolved in 18 mL of a 1:1 mixture of ethanol:acetic acid and stirred at r.t. for 3 days. The resulting crystalline solid was filtered off to yield 1.52 g (77%) of pure (3) m.p. 147-149°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.00 (t, 3H), 3.24 (s, 3H), 3.75 (m, 3H), 3.9 (q, 2H), 4.0 (m, 3H), 4.6 (d, 1H), 5.0 (d, 1H), 7.3 (m, 8H).

*Preparation 3: 4-carboxycubane-1-methylthioxanthylketone*

The thioxanthylcubane adduct (3) (1.69 g, 3.57 mmol) is dissolved in ethanol 33 mL and 8.7 mL of 1 N NaOH and heated at 70°C for 4 h. The resulting solution is evaporated and redissolved in 25 mL of water, acidified with 6 N HCl and extracted with 3 x 50 mL of diethyl ether. The combined organic layers are dried over magnesium sulphate, filtered and concentrated to give a crude product containing (4). Chromatography on silica using ethyl acetate gives 1.26 g (88%) of (4)

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.8 (d, 2H), 3.8 (m, 3H), 4.0 (m, 3H), 4.7 (t, 1H), 7.3 (m, 8H), 9.5 (br, 1H).

*Preparation 4: 4-carboxycubane-1-thioxanthyl-1-(5,5'-hydantoin)*

The thioxanthyl cubane ketone (4) (1.24 g, 3.22 mmol) is dissolved in 1 l ethanol:water (20 mL). Potassium cyanide (0.522 g, 8.0 mmol) and ammonium carbonate (1.39 g, 14.4 mmol) are added and the solution heated in a sealed tube at 85°C for 65 h. The reaction is cooled and acidified with 2 N HCl and extracted with 3 x 40 mL of ethyl acetate. The organic layers are combined, dried over magnesium sulphate, filtered and evaporated to give (5) 1.3 g (88%) as a crude product. This material was hydrolyzed in the next step without purification.

<sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  1.7 (m, 1H), 2.7 (m, 1H), 3.8 (m, 3H), 4.0 (m, 3H), 4.3 (m, 1H), 7.4 (m, 8H).

*Preparation 5: 4-carboxycubane-1- thioxanthyl glycine*





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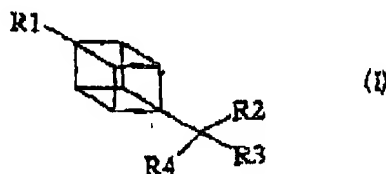
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The hydantoin adduct (5) (300 mg, 0.65 mmol) is taken up in 1 N NaOH (10 mL) and heated at 170 °C for 20 h in a sealed tube. The mixture is cooled and the pH adjusted with 6 N HCl to between 7 and 8. The precipitate formed is filtered and washed with water. The combined filtrate and washings are combined and evaporated to dryness. The resulting residue is purified by column chromatography and finally by reverse phase chromatography to yield (6) as colorless crystals. 70 mg. <sup>1</sup>H NMR (CD<sub>3</sub>OD + D<sub>2</sub>O) δ 2.3 (m, 2H), 3.9 (s, 6H), 4.4 (m, 1H), 7.4 (m, 8H)



We claim:

1. A compound of the formula:



wherein:

R1 can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfinio, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, and -CH<sub>2</sub>-isoxazol;

R2 can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea.

R3 can be H, aliphatic, aromatic or heterocyclic;

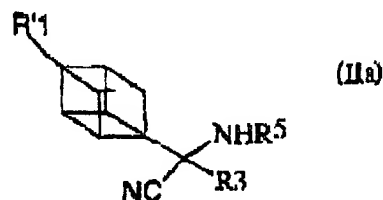
R4 can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol; and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, wherein R1 is COOH.
3. A compound as claimed in claim 1, wherein R2 is NH<sub>2</sub>.
4. A compound as claimed in claim 1, wherein R3 can be -H, or -Me, or xanthyl or thioxanthyl or -CH<sub>2</sub>-xanthyl, or -CH<sub>2</sub>-thioxanthyl and R4 is -COOH.



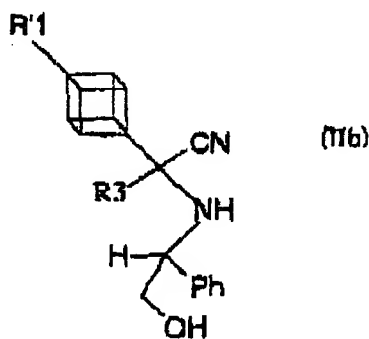
5. A process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolyzing a compound of formula:



wherein:  $R'1$  is an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinyl, borono, tetrazol, isoxazol,  $-CH_2$ -carboxyl,  $-CH_2$ -phosphono,  $-CH_2$ -phosphino,  $-CH_2$ -sulfono,  $-CH_2$ -sulfinyl,  $-CH_2$ -borono,  $-CH_2$ -tetrazol,  $-CH_2$ -isoxazol and higher analogues thereof, or a protected form thereof,  $R3$  can be H, aliphatic, aromatic or heterocyclic and  $R5$  represents a hydrogen atom or an acyl group, and wherein preferred values for  $R5$  are hydrogen and (2-6C) alkanoyl groups, such as acetyl; or

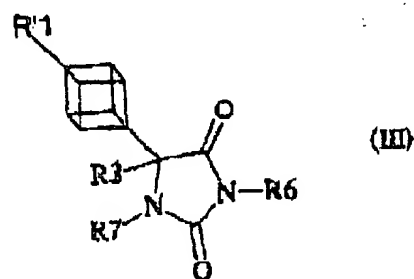
(b) deprotecting and hydrolyzing a compound of formula (II b)



wherein:  $R'1$  and  $R3$  are as defined above; or

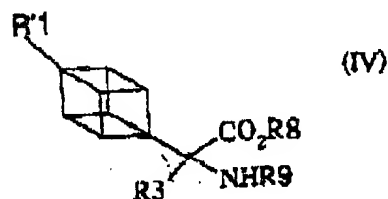


- (c) hydrolyzing a compound of formula:



wherein: R6 and R7 each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof. R'1 and R3 are as defined above; or

- (d) deprotecting a compound of formula:



wherein: R8 represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and R9 represents a hydrogen atom or a nitrogen protecting group, R'1 and R3 are as defined above;

whereafter, if necessary and/or desired:

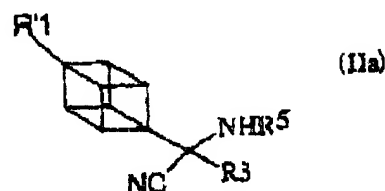
- (i) resolving the compound of Formula I;
- (ii) converting the compound of Formula I into a non-toxic metabolically-labile ester or amide thereof; and/or
- (iii) converting the compound of Formula I or a non-toxic metabolically-labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

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The first part of the paper discusses the importance of the study of the history of the United States. It is argued that a knowledge of the past is essential for a full understanding of the present. The second part of the paper discusses the importance of the study of the history of the world. It is argued that a knowledge of the past is essential for a full understanding of the present. The third part of the paper discusses the importance of the study of the history of the United States. It is argued that a knowledge of the past is essential for a full understanding of the present. The fourth part of the paper discusses the importance of the study of the history of the world. It is argued that a knowledge of the past is essential for a full understanding of the present. The fifth part of the paper discusses the importance of the study of the history of the United States. It is argued that a knowledge of the past is essential for a full understanding of the present. The sixth part of the paper discusses the importance of the study of the history of the world. It is argued that a knowledge of the past is essential for a full understanding of the present. The seventh part of the paper discusses the importance of the study of the history of the United States. It is argued that a knowledge of the past is essential for a full understanding of the present. The eighth part of the paper discusses the importance of the study of the history of the world. It is argued that a knowledge of the past is essential for a full understanding of the present. The ninth part of the paper discusses the importance of the study of the history of the United States. It is argued that a knowledge of the past is essential for a full understanding of the present. The tenth part of the paper discusses the importance of the study of the history of the world. It is argued that a knowledge of the past is essential for a full understanding of the present.

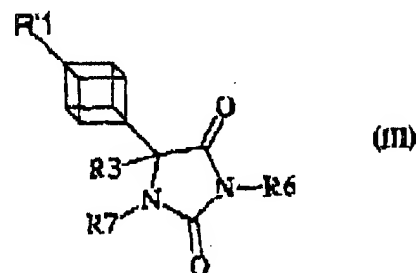


6. A pharmaceutical formulation, which comprises a compound as claimed in claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.
7. A use of the compound according to claim 1 to modulate one or more metabotropic glutamate receptor functions in a warm blooded mammal, wherein said use comprises administering an effective amount of a compound of formula (I) as claimed in claim 1.
8. A compound of formula:



wherein: R'1, R3 and R5 have the meanings as defined in claim 5.

9. A compound of formula:



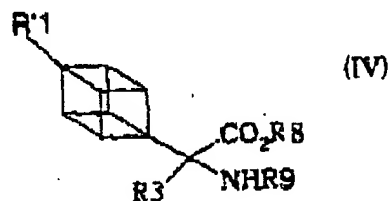
wherein: R'1, R3, R6 and R7 have meanings as defined in claim 5.

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Amended claims



10. A compound of formula:



wherein: R1, R3, R8 and R9 have meanings as defined in claim 5.

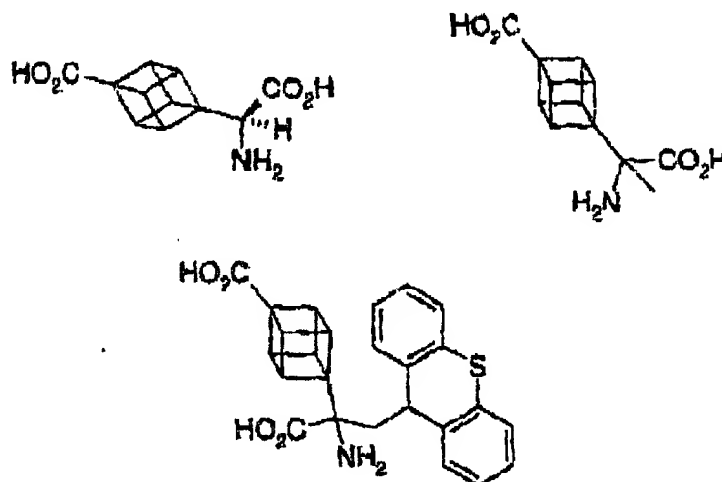
11. A compound according to claim 1, wherein R1 is -COOH, R2 is -NH2, R3 is H and R4 is COOH.
12. A compound according to claim 1, wherein R1 is -COOH, R2 is -NH2, R3 is CH3 and R4 is COOH.
13. A compound according to claim 1, wherein R1 is -COOH, R2 is -NH2, R3 is -CH2-thioxanthyl and R4 is COOH.
14. A use of the compound according to claim 1 for the treatment of a neurological disease or disorder selected from the group comprising: cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia, stroke, cardiac arrest, spinal cord trauma, head trauma, perinatal hypoxia, and hypoglycemic neuronal damage, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, anxiety and related disorders (e.g. panic attack), emesis, brain edema, chronic pain, sleep disorders, Tourette's syndrome, attention deficit disorder, and tardive dyskinesia, wherein said use comprises administering an effective amount of a compound of formula (I).

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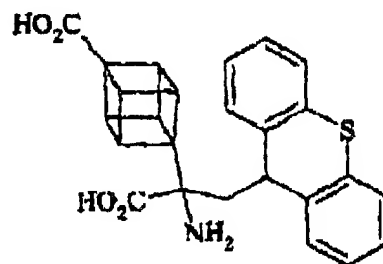
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15. A use of the compound according to claim 1 for the treatment of a psychiatric disease or disorder selected from the group comprising: schizophrenia, anxiety and related disorders (e.g. panic attack), depression, bipolar disorders, psychosis, and obsessive compulsive disorders, wherein said use comprises administering an effective amount of a compound of formula (I).
16. The use according to any one of claims 7, 14 or 15 wherein said compound is selected from the group of compounds comprising:



17. A use of the compound:

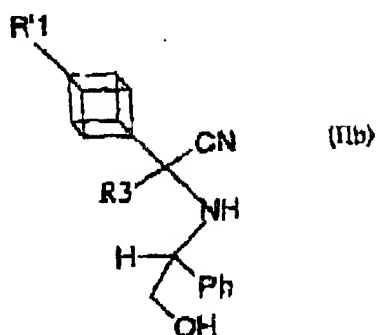


for the treatment of cerebral ischemia, stroke and cardiac arrest, wherein said use comprises administering an effective amount of the said compound.

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18. A compound of formula:



wherein:  $R'1$  and  $R3$  have the meaning as defined in claim 5.

19. A compound according to claim 18, wherein:  $R'1$  is  $-COOMe$ ,  $R3$  is  $H$ .
20. A compound according to claim 9, wherein:  $R'1$  is  $-COOH$ ,  $R3$  is  $CH_3$ ,  $R6 = R7$  is  $H$ .
21. A compound according to claim 9, wherein:  $R'1$  is  $-COOH$ ,  $R3$  is  $-CH_2$ -thioxanthyl,  $R6 = R7$  is  $H$ .

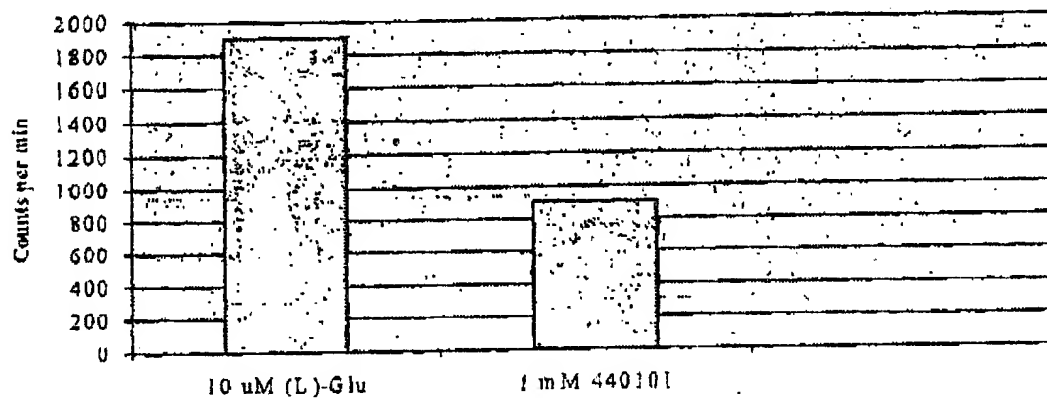
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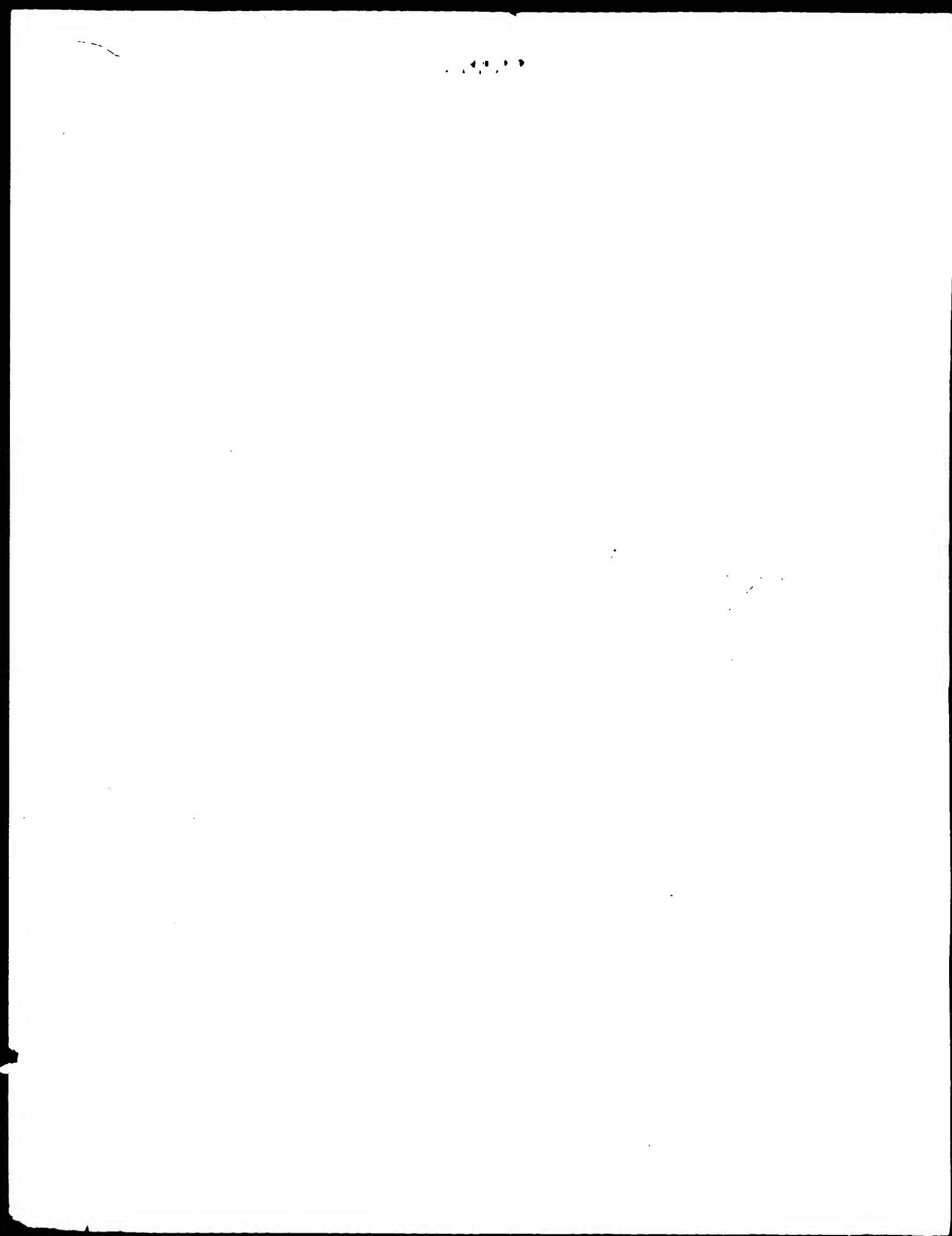




Figure 1

The Actions of a Compound of the Invention as an Antagonist of PI Hydrolysis  
evoked through the mGluR 1 receptor by 10  $\mu$ M (L)-Glu







## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07C 229/48, A61K 31/195, C07D 213/55</b>		<b>A1</b>	(11) International Publication Number: <b>WO 97/19049</b>
			(43) International Publication Date: 29 May 1997 (29.05.97)
(21) International Application Number: <b>PCT/EP96/05079</b>		(74) Common Representative: NOVARTIS AG; Patents & Trade- marks Division, Lichtstrasse 35, CH-4002 Basle (CH).	
(22) International Filing Date: 18 November 1996 (18.11.96)			
(30) Priority Data: 95/A002383      17 November 1995 (17.11.95)      IT		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
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(54) Title: GLYCINE DERIVATIVES			
(57) Abstract			
Compounds of formula (I), wherein R, R <sub>1</sub> , R <sub>2</sub> and X are as defined in the description, are useful as pharmaceuticals.			
<div style="text-align: right;">(I)</div>			

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## GLYCINE DERIVATIVES

The present invention relates to glycine derivatives with affinity to metabotropic glutamate receptors.

Metabotropic glutamate receptors (mGluR) are a family of proteins present in neurons and in the glia, which can interact with glutamate and bring about significant modifications in neurotransmission by interaction with protein G and the resulting regulation of the neosynthesis of second messengers or the modulation of ion channels both at the presynaptic and postsynaptic levels. Recent molecular biology studies have identified at least eight cDNAs which likewise code for mGluR subtypes. In general, on the basis of structural analogies, the effector used and pharmacological properties, it is possible to divide the eight mGluRs into three groups:

- 1st group: comprises mGluR1 and mGluR5 which are capable of stimulating phospholipase C and the inositol cycle. These receptors are stimulated by the antagonists in the following order of power: QUIS> 1S, 3R-ACPD>L-CCG1>>>>L-AP4.
- 2nd group: comprises mGluR2 and mGluR3 which are capable of inhibiting the formation of cAMP induced by forskolin. The order of power of the agonists is as follows: L-CCG1>1S,3R-ACPD>QUIS>>>>L-AP4.
- 3rd group: comprises mGluR4, mGluR6, mGluR7 and mGluR8 which are also capable of inhibiting the formation of cAMP, but in the following order of power: L-AP4>>>1S,3R-ACPD>>>>L-CCG1.

The various mGluRs are differentially distributed in the CNS and several subtypes may coexist in the same area and also in the same neuron. The final effect their activation has depends on the types of receptor present and may therefore be either an inhibitory effect or an

excitatory effect. For example, in the cerebellum, the stimulation of mGluR1 leads to activation of the calcium-dependent potassium channels and therefore to inhibition, whereas, in the hippocampus, activation of mGluR receptors can increase the neuronal excitability by inhibiting the voltage-operated potassium channels. Then there are mGluRs which are localized to the presynaptic level and are capable of regulating the release of the transmitter by means of particularly interesting mechanisms. Thus, the stimulation of mGluR4 or mGluR7 can reduce the influx of  $Ca^{2+}$  into the nerve endings, thereby directly inhibiting the voltage-dependent channels and reducing the synaptic release of transmitter. A similar result can be obtained by stimulating the mGluR2 or mGluR3 receptors, which inhibit the formation of cAMP and in some way reducing the effects of depolarization on the release of the transmitter. In contrast, the stimulation of other mGluR subtypes (mGluR1 and possibly also mGluR5) amplifies the depolarization-release of transmitter combination, especially in the presence of free fatty acids.

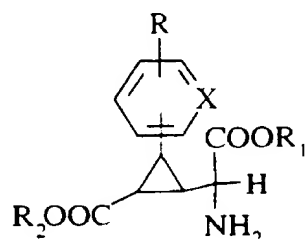
In light of the above, regulation of the functioning of mGluR-controlled neuronal circuits in the hippocampus becomes particularly advantageous. Stimulation of the mGluR4 and mGluR7 receptors reduces transmission at the glutamatergic synapses level, whereas stimulation of mGluR5 can increase the excitability of the circuit, possibly also because it amplifies responses of ionotropic type. The consequences of a reduction in transmission and an increase in excitability are that low-intensity stimuli are blocked, while strong stimuli, capable of overcoming the presynaptic inhibition, are amplified. In this way, the strategic location of the mGluRs leads to the formation of filtering systems capable of increasing the signal/noise ratio of the stimuli which converge on this neuronal circuit. Such systems, in which other types of mGluR also come into play, appear to operate both at the level of phenomena associated with learning and in regulating various

sensory signals (for example in the olfactory pathways). In the basal nuclei, the stimulation of mGluR2 and mGluR3 leads to a considerable reduction in the synaptic release of excitatory transmitter and may affect certain psychic and motor functions. Thus, the pharmacology of mGluRs appears to promise wide fields of therapeutic application since mGluRs appear to have an important role in the processes of neuroprotection and neurodegeneration, in controlling movement, and in the normal functioning of dopaminergic systems, in the onset of epileptic attacks, in the processes of central integration of pain, pressure, visual and sensory stimuli, and in learning. The fact that stimulation of the mGluR receptors can bring about an increase in the sensitivity of the ionotropic receptors for the same transmitter makes these receptors an ideal target for modifying synaptic excitatory functioning.

WO 93/08158 (Suntory Ltd.; 29.4.1993) describes enantiomers of 2-(2,3-dicarboxycyclopropyl)glycine as NMDA-receptor agonists and their therapeutic use as anaesthetics, analgesics and antispastic agents.

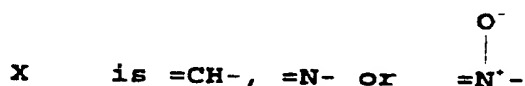
It has now been found that cyclopropylglycine derivatives are endowed with affinity to metabotropic glutamate receptors.

The compounds of the invention have the general formula (I) below



in which

- R is hydrogen, halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>haloalkyl, C<sub>1</sub>-C<sub>4</sub>haloalkoxy, cyano, nitro, -COOR<sub>1</sub> (R<sub>1</sub> being as defined below), -CONR<sub>3</sub>R<sub>4</sub> (R<sub>3</sub> and R<sub>4</sub> independently being hydrogen or C<sub>1</sub>-C<sub>4</sub>alkyl), -PO(OR<sub>1</sub>)<sub>2</sub> (R<sub>1</sub> being as defined below), -SO<sub>2</sub>R<sub>1</sub> (R<sub>1</sub> being as defined below) or -NH-CO-R<sub>5</sub> (R<sub>5</sub> being C<sub>1</sub>-C<sub>4</sub>alkyl or phenyl),
- R<sub>1</sub> and R<sub>2</sub>, independently, are hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl or benzyl, and



- The compounds of formula (I) have four asymmetric centres, which give rise to 16 enantiomers.

The invention comprises the individual enantiomeric forms as well as their racemic or diastereoisomeric mixtures.

- The invention moreover comprises the salts of the compounds (I) with acids or (when R<sub>1</sub> or R<sub>2</sub> = H) bases.

In a group of compounds of formula I, R is hydrogen, an halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>haloalkyl or C<sub>1</sub>-C<sub>4</sub>haloalkoxy, R<sub>1</sub> and R<sub>2</sub> are hydrogen and X is =CH- or =N- in ortho position to the bond which is linked to the cyclopropyl moiety.

Preferred compounds of formula (I) are those in which X is CH and R is hydrogen or a C<sub>1</sub>-C<sub>4</sub>alkoxy group.

- Examples of C<sub>1</sub>-C<sub>4</sub>alkyl groups include methyl, ethyl, n-propyl, isopropyl and isobutyl, preferably methyl.

Examples of C<sub>1</sub>-C<sub>4</sub>alkoxy groups include methoxy, ethoxy, n-propoxy and isopropoxy, preferably methoxy.

- Examples of C<sub>1</sub>-C<sub>4</sub>haloalkyl groups include trifluoromethyl and pentafluoroethyl, preferably trifluoromethyl.

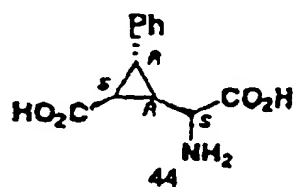
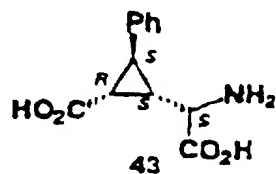
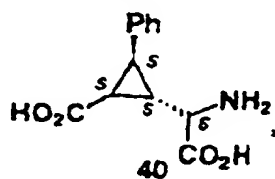
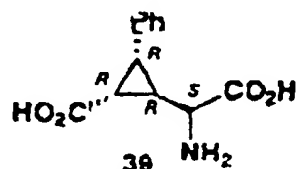
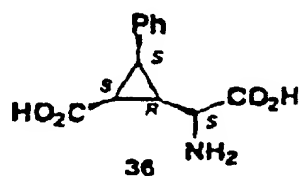
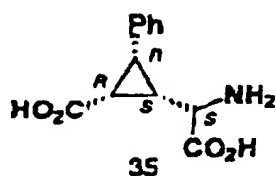
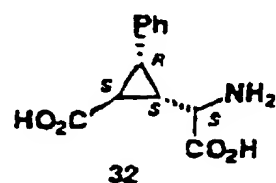
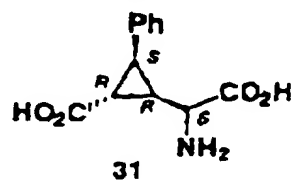
Examples of C<sub>1</sub>-C<sub>4</sub>haloalkoxy groups include trifluoromethoxy and difluoromethoxy, preferably tri-



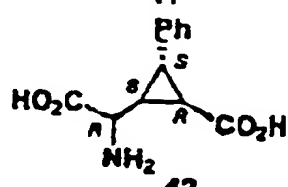
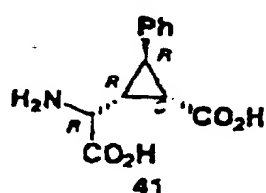
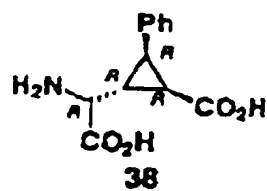
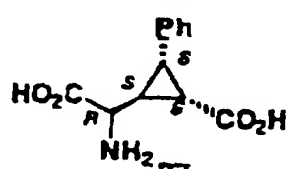
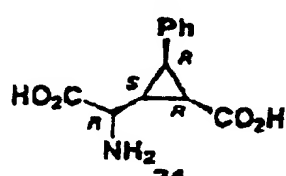
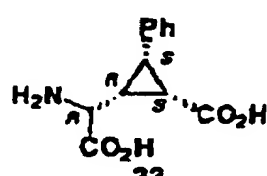
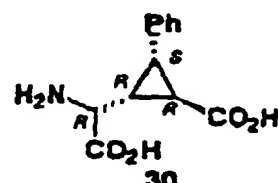
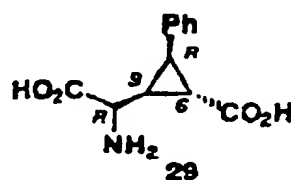
fluoromethoxy.

The formulae of 16 possible enantiomers of the compounds of formula (I) in which R is H, X is =CH- and R<sub>1</sub> is hydrogen are given below. The S configuration of  
5 the carbon atom of the glycine residue is preferred and the configuration of compound 44 is particularly preferred.

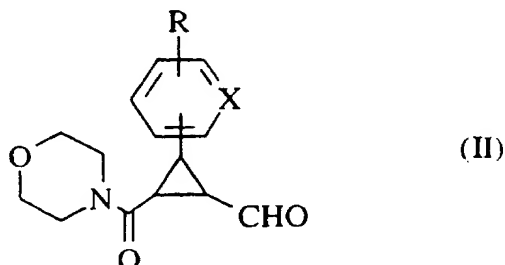
## S Series



## R Series



The compounds of formula I wherein  $R_1$  and  $R_2$  are H may be prepared by reaction of a compound of formula (II)



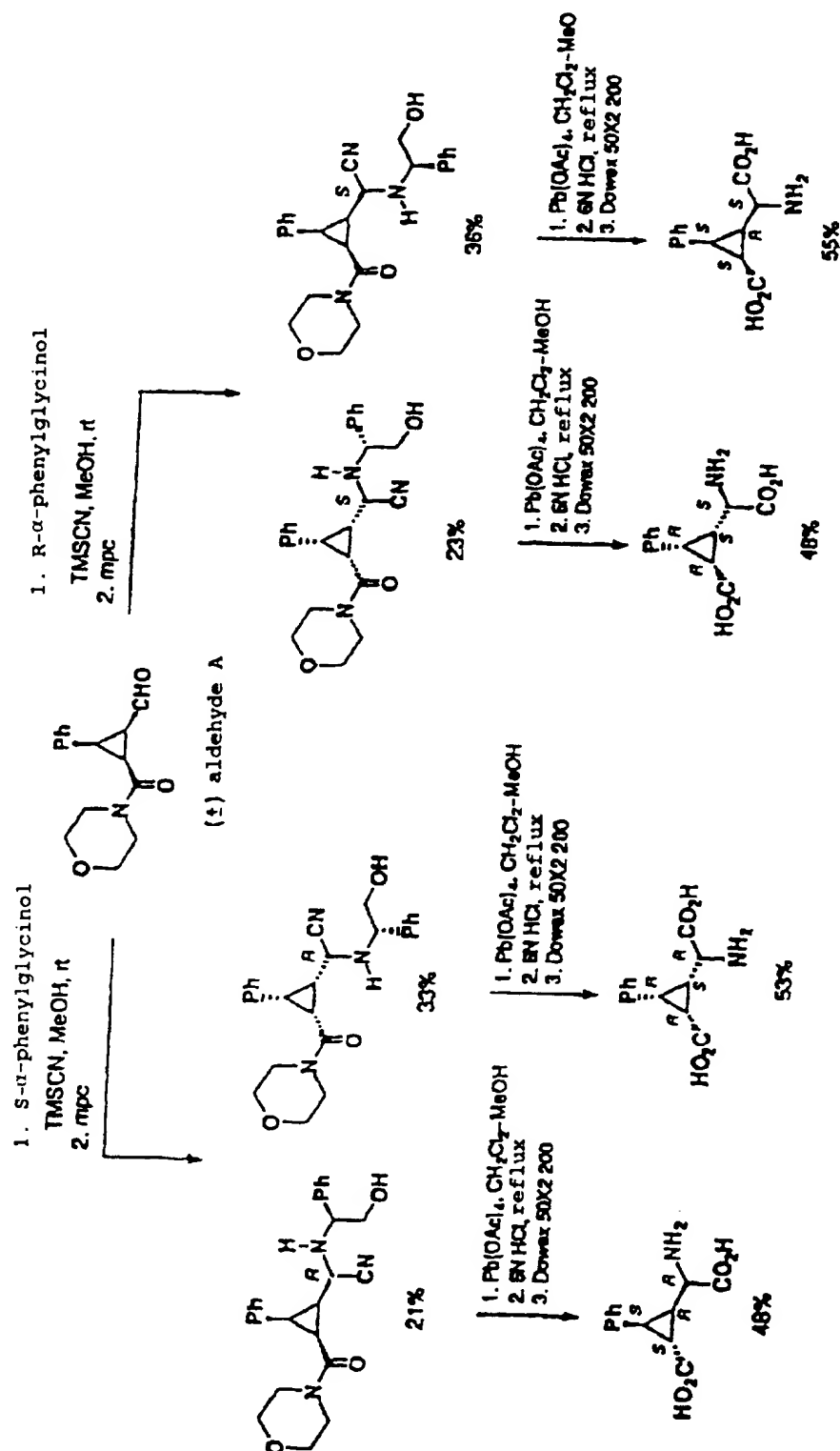
in which X and R are as defined above, with  $\alpha$ -phenylglycinol and then with TMSCN, followed by oxidative cleavage with lead tetraacetate and acid hydrolysis. The compounds wherein  $R_1$  and/or  $R_2$  are alkyl or benzyl can be prepared from the free acids according to well known procedures.

By using various enantiomers of the aldehydes (II) and of R- or S- $\alpha$ -phenylglycinol, the desired enantiomers may be prepared.

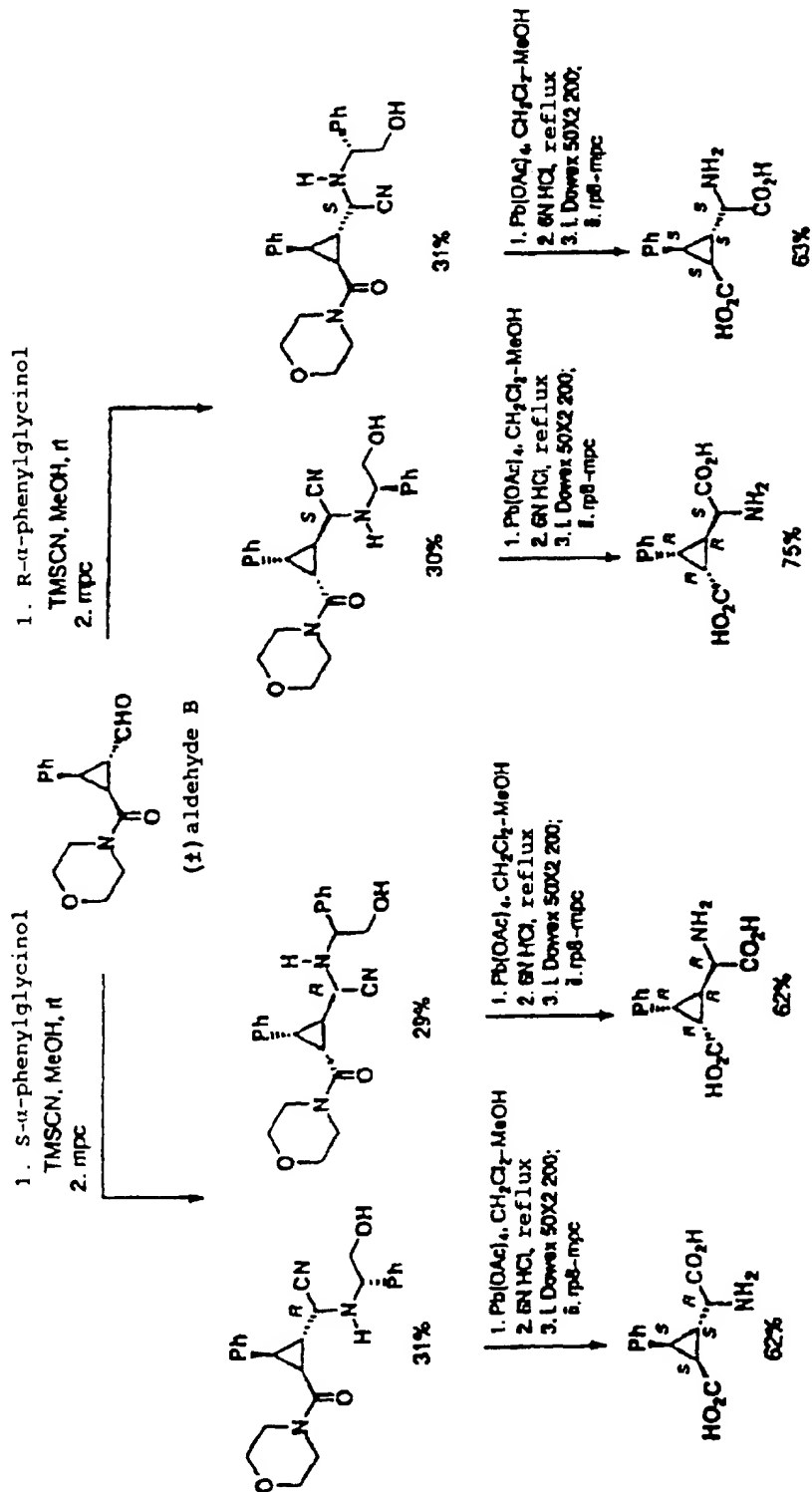
Schemes 1-4 for the preparation of compounds (I) in which  $X = CH$  and  $R = H$  are given below. Further compounds (I) can be obtained by identical methods, starting with appropriate aldehydes (II).

Aldehydes (II) can be prepared according to the following schemes 5 and 6, again with reference to compounds in which X is CH and R is hydrogen. Obviously, further aldehydes of formula (II) can be prepared in a similar manner, starting with the appropriate E-cinnamyl or E-pyridylvinyl alcohols.

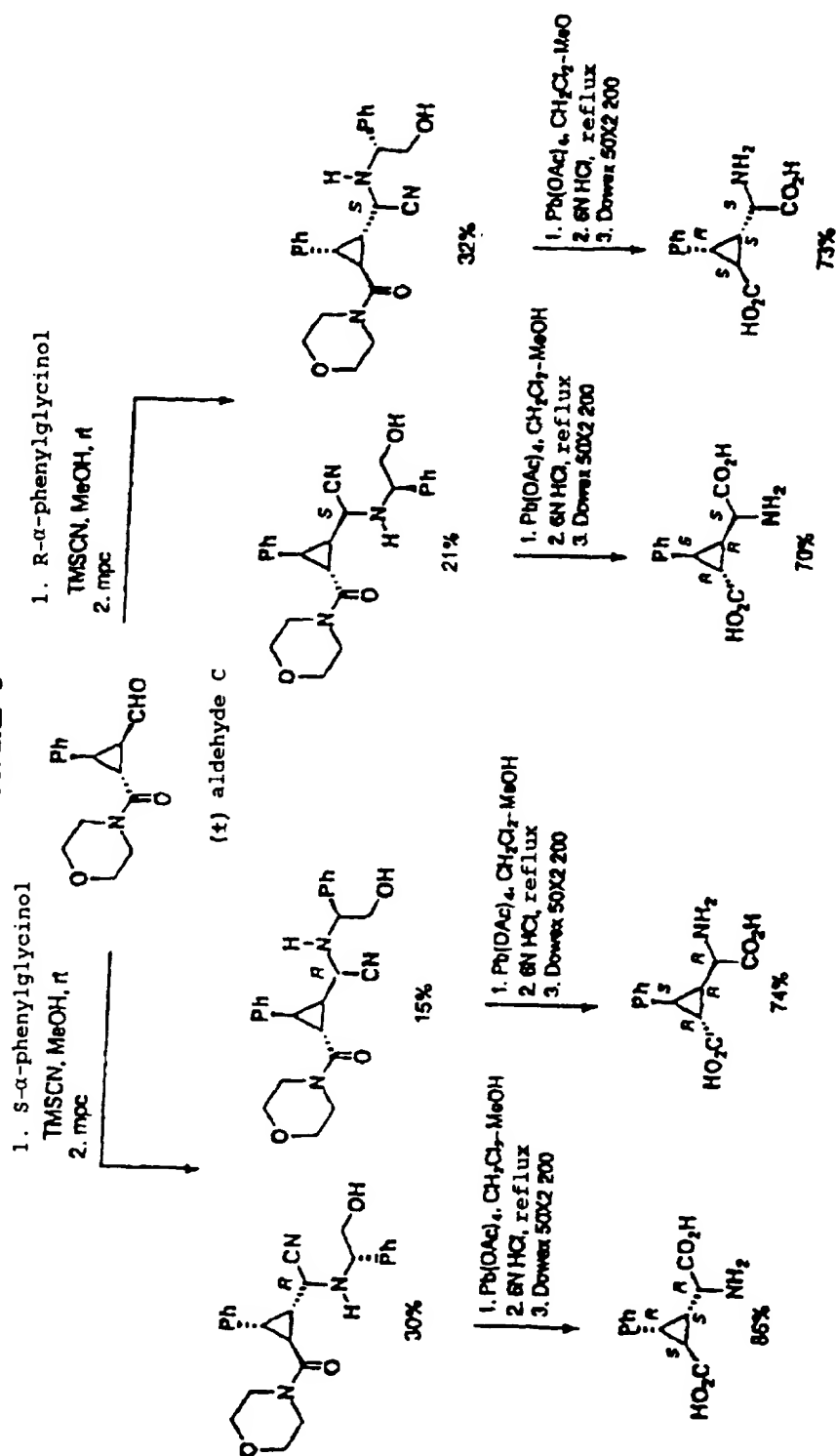
SCHEME 1



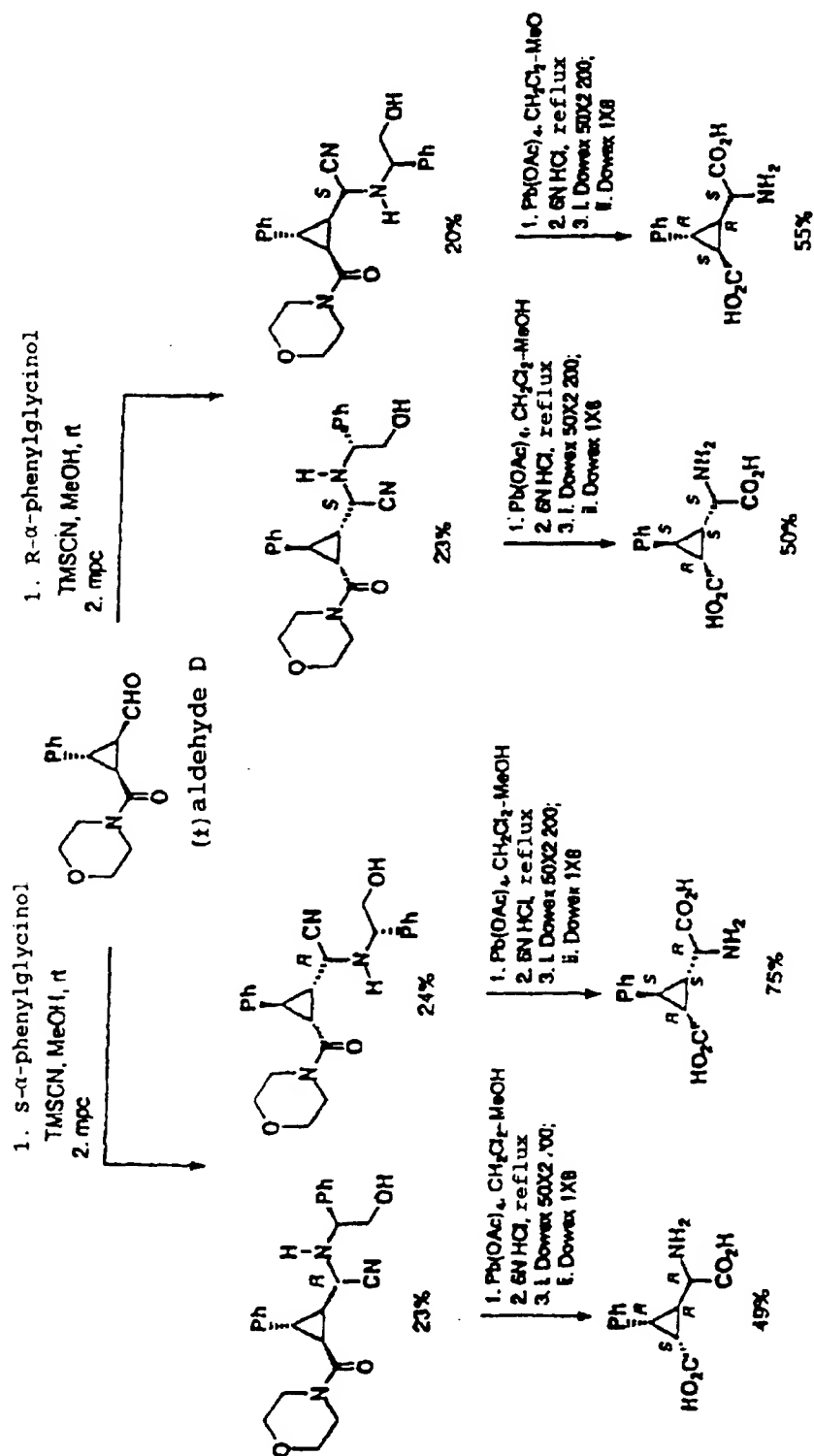
SCHEME 2



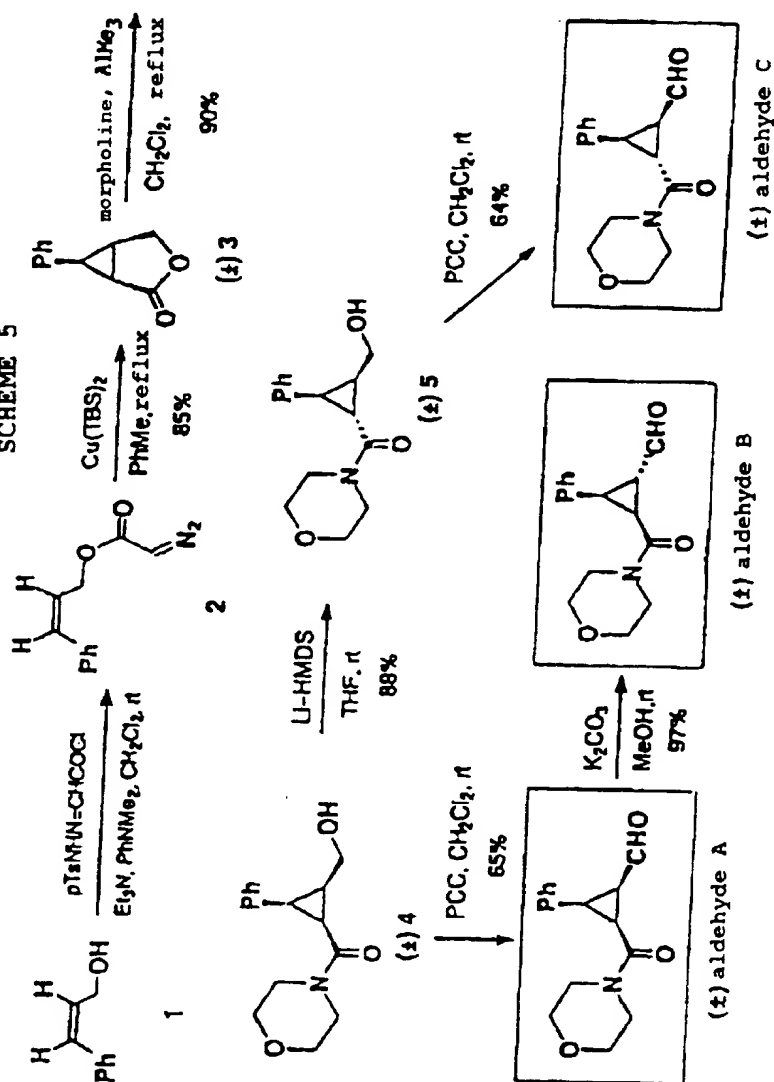
SCHEME 3



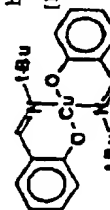
SCHEME 4



SCHEME 5



bis(N-t-Bu-salicylaldiminato) copper (II)  
 [E. J. Corey, et al., Tetrahedron Lett. 1984, 25, 3559]



$\text{Cu(TBS)}_2 =$





The compounds of formula (I) and their pharmaceutically acceptable salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro, particularly affinity to metabotropic glutamate receptors (mGluRs) as indicated above, and are therefore useful as pharmaceuticals.

The agents of the invention were evaluated as mGluR antagonists in the following tests:

- 1) Antagonism of the phospholipase C-stimulatory action by 1S,3R-ACPD (300  $\mu$ M) on slices of rat cortex. Active molecules in this test are considered to be mGluR1 or mGluR5 antagonists (group 1).
- 2) Antagonism of the action of L-CCG1 (3  $\mu$ M) on the formation of cAMP induced by forskolin (30  $\mu$ M) on slices of rat stria. Active molecules in this test are considered to be mGluR2 or mGluR3 antagonists (group 2).
- 3) Antagonism of the action of L-AP4 (10  $\mu$ M) on the formation of cAMP induced by forskolin (30  $\mu$ M) on slices of rat cerebellum. Active molecules in this test are considered to be mGluR4, mGluR7 and mGluR8 antagonists (group 3).

The agents of the invention show significant activity in these tests at about 0.01 to about 100 $\mu$ M.

The molecules active on group 1 mGluRs were then tested for their potentiation of the release of transmitter from slices of cortex and the molecules active on group 2 were tested for their inhibition of the release of transmitter from slices of rat stria. The methods used for the experiments reported above are described in: Lombardi et al. *British J. Pharmacol.* 19933, 110, 1407-1412.

The agents of the invention, and in particular compound 44, display selective antagonist activity towards the mGluRs of the second group by antagonizing the effect of L-CCG-1 on the production of cAMP and on the release of transmitter from slices of stria, with an  $IC_{50}$  of 10  $\mu$ M. The effect is selective since the action of

1S, 3R ACDP on phospholipase C is not modified.

Furthermore, the compounds of the invention may act as mGluR-agonists. Agonistic activity can be shown in the following way:

- 5 1) Stimulation of phospholipase C in BHK cells which are transfected with mGluRs of group I;
- 2) Decrease of forskolin-stimulated cAMP-formation in transfected BHK cells expressing one of the mGluRs of class II or III.

10 The agents of the invention show significant activity in these tests at about 0.01 to about 100µM. Compound 44, for example, acts as an agonist at mGluR4 with an EC50 < 200 µM.

The compounds of the invention are therefore  
15 useful in disorders which are linked to metabotropic excitatory amino acid receptors. Such disorders include cerebral ischemia (e.g. due to stroke or cardiac arrest during bypass surgery), head trauma, subarachnoid haemorrhage, Alzheimers disease, Huntingtons Chorea,  
20 amyotrophic lateral sclerosis, AIDS-induced dementia, Parkinson syndrom, convulsive disorders (e.g. epilepsy), muscular spasms, chronic and neuropathic pain, cognitive disorders such as memory deficits, schizophrenia, anxiety, emesis and drug abuse.

25 For the therapeutic uses envisaged, the compounds of the invention will be formulated in appropriate dosage forms, using conventional techniques and excipients. The dosage will be determined by the doctor in charge, based on the pharmaceutical and pharmacodynamic properties of  
30 the compounds. An indicated daily dosage will lie within the range from about 1 mg to about 1g, conveniently administered, for example, in divided doses up to four times a day.

In accordance with the foregoing, the present  
35 invention also provides a pharmaceutical composition comprising an agent of the invention, in association with a pharmaceutical carrier or diluent.

The invention furthermore provides an agent of the invention for use as a pharmaceutical, particularly

in disorders linked to metabotropic glutamate receptors, e.g. in the treatment of the above-mentioned disorders.

Moreover the present invention provides the use of an agent of the invention for the manufacture of a medicament for the treatment of the above-mentioned disorders.

In still a further aspect the invention provides a method for the treatment of disorders linked to metabotropic glutamate receptors, e.g. for the above-mentioned disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The examples which follow further illustrate the invention.

Example 1.

(2S,1'S,2'S,3'R)-2-(2'-carboxy-3'-phenylcyclopropyl)-glycine

a) 6-Phenyl-3-oxabicyclo[3.1.0]hexan-2-one

A solution of cis-3-phenyl-2-propen-1-yl diazoacetate (1 g, 4.95 mmol) in anhydrous toluene (165 ml) was added to a refluxing solution of bis(N-t-butylsalicylaldiminato)copper (II) (0.104 g, 0.25 mmol) in anhydrous toluene (165 ml) with stirring under an argon atmosphere for 12 hours. After cooling, the reaction mixture was evaporated and the residue subjected to flash chromatography, eluting with petroleum ether containing from 10 to 40% of ethyl acetate, to give the title compound. (0.75 g, 87%), m.p. 112-3°C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.60 (2H, m, 1-CH and 5-CH), 2.78 (1H, t, J=8.8 Hz, 6-CH), 4.05 (1H, dd, J=0.6 Hz, J=9.8 Hz, 4-CH<sub>a</sub>), 4.35 (1H, dt, J=2.7 Hz, J=9.8 Hz, 4-CH<sub>b</sub>), 7.20-7.35 (5H, m, aromatic)

b) 2-Hydroxymethyl-3-phenylcyclopropanecarboxylic acid (4-morpholinyl)amide

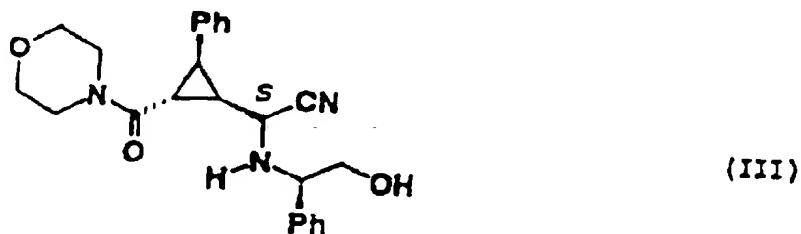
A 2.0 M solution of trimethylaluminium in hexane (22.35 ml) was added dropwise over 20 minutes to a solution of morpholine (3.9 ml) in anhydrous CH<sub>2</sub>Cl<sub>2</sub>,

- (108 ml) with stirring at room temperature under an argon atmosphere. The stirring was continued for 20 minutes after the addition of a solution of the compound obtained in a) (2.59 g, 14.88 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (67 ml) over 20 minutes, and the resulting mixture was then heated at 40°C for 20 hours. The reaction mixture was acidified cautiously with 1N HCl, the organic phase was separated out and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 60 ml). The combined organic phases were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and, after evaporation of the solvent, the residue (3.7 g) was subjected to flash chromatography, eluting with  $\text{CH}_2\text{Cl}_2$ /methanol (95/5) to give the title compound. (3.50 g, 90%), m.p. 103°C;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.00 (2H, m, 1-CH and 2-CH), 2.50 (1H, t,  $J=5.5$  Hz, 3-CH), 3.40-3.80 (8H, m, morpholine), 3.90-4.15 (2H, m,  $\text{CH}_2\text{OH}$ ), 7.15-7.40 (5H, m, aromatic)
- c) A solution of the compound obtained in b) (3.40 g, 13.03 mmol) in anhydrous tetrahydrofuran (200 ml) was added dropwise over 30 minutes to a solution of lithium hexamethyldisilazide, prepared by adding a 1.5 M solution of butyllithium in hexane (26 ml) to a solution of anhydrous hexamethyldisilazane (8.3 ml) in tetrahydrofuran (200 ml). The addition was carried out at room temperature under an argon atmosphere. Stirring was continued for 1 hour, after which the reaction mixture was diluted with saturated  $\text{NH}_4\text{Cl}$  (500 ml) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 200 ml). The combined organic extracts were then dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give a residue which was subjected to flash chromatography, eluting with  $\text{CH}_2\text{Cl}_2$ /methanol (95/5) to give the epimer of the compound obtained in b). (3.00 g, 88%);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.05 (2H, m, 2-CH and OH), 2.25 (1H, t,  $J=5.0$  Hz, 1-CH), 2.85 (1H, dd,  $J=5.0$  Hz,  $J=12.0$  Hz, 3-CH), 3.50-3.90 (8H, m, morpholine ring), 3.85 (2H, dd,  $J=6.7$  Hz,  $J=12.0$  Hz,  $\text{CH}_2\text{OH}$ ), 7.15-7.40 (5H, m, aromatic).

- d) 2-Formyl-3-phenylcyclopropanecarboxylic acid  
(4-morpholinyl)amide

PCC (4.20 g, 19.48 mmol) was added to a solution of  
the compound obtained in c) (3.00 g, 11.49 mmol) in  
5 anhydrous  $\text{CH}_2\text{Cl}_2$  (130 ml) and the resulting mixture  
was stirred at room temperature under an argon  
atmosphere for 16 hours. The reaction mixture was  
then diluted with ethyl ether and filtered and the  
solvent was evaporated off. Flash chromatography of  
10 the residue and elution with ethyl acetate/petroleum  
ether (8/2) gave the title compound. (1.90 g, 64%),  
m.p. 89°C;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.78-2.90 (1H, m, 2-CH),  
3.12 (1H, t,  $J=4.9$  Hz, 1-CH), 3.35 (1H, dd,  
 $J=6.4$  Hz,  $J=9.4$  Hz, 3-CH), 6.60-3.90 (8H), m, mor-  
15 pholine ring, 7.18-7.40 (5H, m, aromatic), 9.20 (1H,  
d,  $J=5.1$  Hz, CHO).

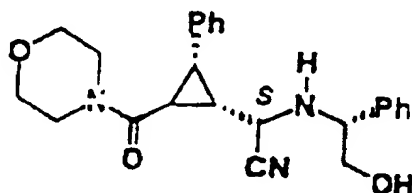
- e) R-Phenylglycine (0.45 g, 3.28 mmol) was added to a  
solution of the aldehyde (0.85 g, 3.28 mmol) in  
methanol (32.8 ml) and the resulting mixture was  
20 stirred at room temperature for 2 hours. After  
cooling to 0°C, TMSCN (0.65 g, 6.56 mmol) was added  
and the resulting mixture was stirred for 12 hours  
at room temperature. Evaporation of the solvent gave  
a residue which was subjected to medium-pressure  
25 chromatography, eluting with  $\text{CH}_2\text{Cl}_2$ /methanol (98/2)  
to give the compound of formula:



(3.00 g, 2%), m.p. 123-4°C  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.20 (2H,  
m,  $\text{CHCO}$  and  $\text{CH-CHN}$ ), 2.80 (1H, d,  $J=9.6$  Hz,  $\text{CHCN}$ ),  
3.10 (2H, m,  $\text{CHPh}$  and  $\text{OH}$ ), 3.40-3.90 (10H, m, mor-  
30 pholine and  $\text{CH}_2\text{OH}$ ), 3.95 (1H, dd,  $J=3.8$  and 13.5 Hz,  
 $\text{CH-CH}_2\text{OH}$ ), 6.70-7.40 (10H, 2 x m, aromatic).

Subsequent elution with the same solvent gave the

compound of formula



(IV)

(0.450 g, 33%), m.p. 146-7°C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.25 (2H, m, CHCO and CH-CHN), 2.60 (1H, d, J=8.0 Hz, CHCN), 2.90 (2H, m, CHPh and OH), 3.50-4.00 (11H, m, morpholine, CH<sub>2</sub>OH and CH-CH<sub>2</sub>OH), 6.90-7.40 (10H, 2 x m, aromatic).

f) (2S,1'S,2'S,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)glycine

Lead tetraacetate (0.360 g, 0.81 mmol) was added to a solution of the compound obtained in e), formula (IV) (0.300 g, 0.74 mmol) in an anhydrous methanol/methylene chloride mixture (12 ml, 1/1); after 10 minutes, water (10 ml) was added and the resulting mixture was filtered through Celite. After evaporation of the solvent, the residue was refluxed in 6N HCl (30 ml) for 12 hours. The reaction mixture was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 ml) and evaporated. The residue was subjected to chromatography on an ion exchange resin of Dowex 50 x 2 200 type: elution with 10% pyridine gave the title compound. (0.110 g, 63%), m.p. 221°C; <sup>1</sup>H-NMR (D<sub>2</sub>O+DCI) δ 2.15 (1H, td, J=5.2 and 9.3 Hz, 1'-CH), 2.50' (1H, t, J=5.2 Hz, 2'-CH), 3.05 (1H, dd, J=5.2 and 9.3 Hz, 3'-CH), 3.20 (1H, d, J=10.2 Hz, 2-CH), 7.30 (5H, br s, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 22.90 (C-1'), 27.76 (C-2'), 31.33 (C-3') 51.50 (C-2), 127.66, 128.57, 128.57, 128.94, 133.26 (aromatic), 169.69, 175.27 (CO); [α]<sub>D</sub><sup>20</sup>-108 (c 0.15, 2.5N HCl).

#### Example 2

In a similar manner to Example 1, starting with the appropriate aldehydes of formula (II) and using, depending on the case, R- or S-α-phenylglycinol as

indicated in the above schemes 1-4, the following compounds were obtained:

- (2R,1'S,2'S,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 86% yield; m.p. 240-1°C; <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 1.95 (1H, td, J=5.4, 8.9 and 10.8 Hz, 1'-CH), 2.55 (1H, t, J=5.4 Hz, 2'-CH), 2.85 (1H, dd, J=5.4 and 8.9 Hz, 3'-CH), 3.00 (1H, d, J=10.8 Hz, 2-CH), 7.20-7.35 (5H, m, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 23.90, 27.78, 29.97, 50.40, 128.03, 128.43, 129, 17, 132.76, 170.81, 175.24; [α]<sub>D</sub><sup>20</sup> -74 (c 0.30, 2.5N HCl).
- (2R,1'R,2'R,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 74% yield; m.p. 221-3°C; <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 2.10 (1H, dt, J=5.0 and 10.5 Hz, 1'-CH), 2.40 (1H, t, J=5.0 Hz, 2'-CH), 3.00 (2H, m, 3'-CH and 2-CH), 7.30 (5H, d, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 22.91, 27.83, 31.39, 51.49, 127.69, 128.59, 128.96, 133.28, 169.70, 175.25; [α]<sub>D</sub><sup>20</sup> +100 (c 0.20, 2.5N HCl).
- (2S,1'R,2'R,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; 70% yield; [α]<sub>D</sub><sup>20</sup> +72 (c 0.30, 2.5N HCl).
- (2R,1'R,2'S,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 48% yield; m.p. 219-220°C; <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 1.80 (1H, dt, J=9.4 and 11.9 Hz, 1'-CH), 2.49 (1H, t, J=9.4 Hz, 2'-CH), 2.75 (1H, t, J=9.4 Hz, 3'-CH), 4.10 (1H, d, J=11.9 Hz, 2-CH), 7.10-7.30 (5H, m, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 23.99, 24.54, 28.51, 49.00, 127.86, 129.20, 129.71, 133.33, 171.27, 175.24; [α]<sub>D</sub><sup>20</sup> +20 (c 0.50, 2.5N HCl).
- (2R,1'S,2'R,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 53% yield; m.p. 219-220°C; <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 1.90 (1H, dt, J=8.8 and 11.5 Hz, 1'-CH), 2.55 (1H, t, J=8.8 Hz, 2'-CH), 2.80 (1H, t, J=8.8 Hz, 3'-CH), 4.15 (1H, d, J=11.5 Hz, 2-CH), 7.10-7.30 (5H, m, aromatic); <sup>13</sup>C-NMR (D<sub>2</sub>O+DCI) δ 23.46, 24.20, 28.54, 49.16, 127.61, 128.95, 129.49, 132.94, 171.05, 173.98; [α]<sub>D</sub><sup>20</sup> -17 (c 0.60, 2.5N HCl).
- (2S,1'S,2'R,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; 48% yield; [α]<sub>D</sub><sup>20</sup> -21 (c 0.50, 2.5N HCl).
- (2S,1'R,2'S,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; 55% yield; [α]<sub>D</sub><sup>20</sup> +18 (c 0.40, 2.5N HCl).

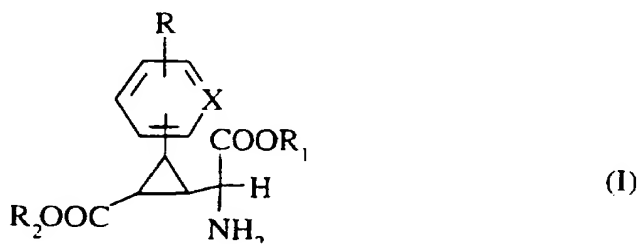


(2S,1'S,2'S,3'R)-2-(2'-Carboxy-3'-o-methoxyphenyl-cyclopropyl)glycine.

(0.100 g, 82%), m.p. 219-20°C; <sup>1</sup>H-NMR (D<sub>2</sub>O+DCI) δ 2.15 (1H, td, J=5.8 and 10.3 Hz, 1'-CH), 2.40 (1H, t, J=5.8 Hz, 2'-CH), 2.9-3.10 (2H, m, 3'-CH and 2-CH), 3.80 (3H, s, OMe), 6.90-7.40 (4H, m, aromatic); [α]<sub>D</sub><sup>20</sup> -81 (c 0.15, 2.5N HCl).

## CLAIMS

1. A compound of formula I

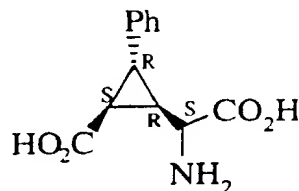


wherein

- 5 R is hydrogen, halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>haloalkyl, C<sub>1</sub>-C<sub>4</sub>haloalkoxy, cyano, nitro, -COOR<sub>1</sub> (R<sub>1</sub> being as defined below), -CONR<sub>3</sub>R<sub>4</sub> (R<sub>3</sub> and R<sub>4</sub> independently being hydrogen or C<sub>1</sub>-C<sub>4</sub>alkyl), -PO(OR<sub>1</sub>)<sub>2</sub> (R<sub>1</sub> being as defined below), -SO<sub>3</sub>R<sub>1</sub> (R<sub>1</sub> being as defined below) or -NH-CO-R<sub>5</sub> (R<sub>5</sub> being C<sub>1</sub>-C<sub>4</sub>alkyl or phenyl), R<sub>1</sub> and R<sub>2</sub>, independently, are hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl or benzyl, and
- 10
- 15 X is =CH-, =N- or  $\begin{array}{c} \text{O}^- \\ | \\ =\text{N}^+ \end{array}$  or a salt thereof.

2. A compound of formula I according to claim 1 wherein R is hydrogen, an halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>haloalkyl or C<sub>1</sub>-C<sub>4</sub>haloalkoxy, R<sub>1</sub> and R<sub>2</sub> are hydrogen and X is =CH- or =N- in ortho position to the bond which is linked to the cyclopropyl moiety, or a salt thereof.
- 20
- 25 3. A compound of claim 1 wherein R is hydrogen or C<sub>1</sub>-C<sub>4</sub>alkyl, R<sub>1</sub> and R<sub>2</sub> are hydrogen and X is =CH-.

4. The compound of formula



and its salts.

5. A compound of anyone of claims 1 to 4, in free or pharmaceutically acceptable salt form, for use as a pharmaceutical.
6. A compound of anyone of claims 1 to 4, in free or pharmaceutically acceptable salt form, for use in disorders linked to metabotropic glutamate receptors.
7. A compound of anyone of claims 1 to 4, in free or pharmaceutically acceptable salt form, for use in the treatment of cerebral ischemia, head trauma, subarachnoid haemorrhage, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, Parkinson syndrome, convulsive disorders, muscular spasms, pain, cognitive disorders, schizophrenia, anxiety, emesis and drug abuse.
8. A pharmaceutical composition comprising a compound of anyone of claims 1 to 4 in free or pharmaceutically acceptable salt form, in association with a pharmaceutical carrier or diluent.
9. The use of a compound of anyone of claims 1 to 4 in free or pharmaceutically acceptable salt form, as a pharmaceutical for the treatment of disorders linked to metabotropic glutamate receptors.

10. The use of a compound of anyone of claims 1 to 4 in  
free or pharmaceutically acceptable salt form, for  
the manufacture of a medicament for the treatment of  
disorders linked to metabotropic glutamate  
receptors.

5

11. A method for the treatment of disorders linked to  
metabotropic glutamate receptors in a subject in  
need of such treatment, which comprises  
administering to such subject a therapeutically  
effective amount of a compound of anyone of claims  
1 to 4 in free or pharmaceutically acceptable salt  
form.

10

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/EP 96/05079A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07C229/48 A61K31/195 C07D213/55

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BIOORG. MED. CHEM. LETT. (1996), 6(18), 2243-2246 CODEN: BMCLE8; ISSN: 0960-894X, 1996, XP000617002 MARINOZZI, MAURA ET AL: "Asymmetric synthesis of enantiomerically pure (2S,1'S,2'S,3'R)- phenylcarboxycyclopropylglycine (PCCG-4): a potent and selective ligand at group II metabotropic glutamate receptors" see the whole document --- -/--	1-11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \* "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

30 January 1997

Date of mailing of the international search report

10.02.97

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# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/EP 96/05079

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	MOL. PHARMACOL. (1996), 50(1), 6-9 CODEN: MOPMA3;ISSN: 0026-895X, 1996, XP000617009 THOMSEN, CHRISTIAN ET AL: "(2S,1'S,2'S,3'R)-2-(2'-carboxy-3'-phenylcyclopropyl)glycine, a potent and selective antagonist of type 2 metabotropic glutamate receptors" see the whole document ---	1-11
P,X	J. MED. CHEM. (1996), 39(11), 2259-69 CODEN: JMCMAR;ISSN: 0022-2623, 1996, XP000617011 PELLICCIARI, ROBERTO ET AL: "Synthesis and Pharmacological Characterization of All Sixteen Stereoisomers of 2-(2'-Carboxy-3'-phenylcyclopropyl)glycine . Focus on (2S,1'S,2'S,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)glycine, a Novel and Selective Group II Metabotropic Glutamate Receptor Antagonist" see page 2261 ---	1-11
A	US 4 959 493 A (OHFUME YASUFUMI ET AL) 25 September 1990 see claims ---	1-11
A	WO 93 08158 A (SUNTORY LTD) 29 April 1993 see claims ---	1-11
A	EP 0 363 994 A (SUNTORY LTD) 18 April 1990 see claims ---	1-11
A	PATENT ABSTRACTS OF JAPAN vol. 018, no. 520 (C-1255), 30 September 1994 & JP 06 179643 A (SUNTORY LTD), 28 June 1994, see abstract ---	1-11
A	PATENT ABSTRACTS OF JAPAN vol. 016, no. 066 (C-0912), 19 February 1992 & JP 03 261748 A (SUNTORY LTD), 21 November 1991, see abstract -----	1-11

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 96/05079

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4959493	25-09-90	CA-A- 1305177 JP-A- 1093563 JP-B- 7068192	14-07-92 12-04-89 26-07-95
WO-A-9308158	29-04-93	AT-T- 137215 DE-D- 69210214 DE-T- 69210214 EP-A- 0564658 JP-T- 6504553 US-A- 5334757	15-05-96 30-05-96 02-10-96 13-10-93 26-05-94 02-08-94
EP-A-0363994	18-04-90	JP-A- 2108654 DE-D- 68909362 DE-T- 68909362 ES-T- 2059669 US-A- 5068412	20-04-90 28-10-93 10-03-94 16-11-94 26-11-91



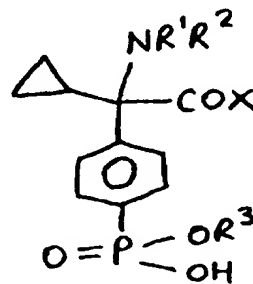


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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07F 9/38, A61K 31/66, C07F 9/40</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/21715</b> <b>(43) International Publication Date:</b> 19 June 1997 (19.06.97)
<b>(21) International Application Number:</b> PCT/GB96/03073 <b>(22) International Filing Date:</b> 12 December 1996 (12.12.96) <b>(30) Priority Data:</b> 9525416.5                      13 December 1995 (13.12.95)      GB <b>(71) Applicants (for all designated States except US):</b> UNIVERSITY OF BRISTOL [GB/GB]; Senate House, Tyndall Avenue, Bristol BS8 1TH (GB). TOCRIS COOKSON LIMITED [GB/GB]; Churchill Building, Langford House, Langford, Bristol BS18 2DY (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> WATKINS, Jeffrey, Clifton [GB/GB]; 8 Lower Court Road, Lower Almondsbury, Bristol BS12 8DW (GB). JANE, David, Edward [GB/GB]; 123 Redland Road, Redland, Bristol BS6 6QX (GB). <b>(74) Agent:</b> STEVENS, Ian, Edward; Stevens Hewlett & Perkins, 1 St. Augustine's Place, Bristol BS1 4UD (GB).		<b>(81) Designated States:</b> US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> ALPHA-CYCLOPROPYL-SUBSTITUTED PHENYLGLYCINES AS CNS AGENTS  <b>(57) Abstract</b>  Compounds of formula (I) are provided wherein: R <sup>1</sup> and R <sup>2</sup> are independently selected from hydrogen, optionally substituted alkyl and optionally substituted acyl; R <sup>3</sup> is hydrogen or an optionally substituted group selected from alkyl, aryl and aralkyl; and X is OR <sup>6</sup> , where R <sup>6</sup> is hydrogen or optionally substituted alkyl, or NR <sup>4</sup> R <sup>5</sup> , where R <sup>4</sup> and R <sup>5</sup> are independently selected from hydrogen and optionally substituted alkyl, optionally substituted on the phenyl ring. The compounds have activity at receptor sites in the central nervous system.		



(I)

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
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GA	Gabon			VN	Viet Nam

ALPHA-CYCLOPROPYL-SUBSTITUTED PHENYLGLYCINES AS CNS  
AGENTS

5 This invention relates to compounds having activity at receptor sites in the central nervous system (CNS). In particular, the invention relates to phenylglycine derivatives which have a cyclopropyl group at the  $\alpha$ -position and to pharmaceutical compositions comprising these compounds.

10 Various amino acids have recently become of interest following the discovery that they are able to influence the activity of certain receptor sites in the CNS and attention has been directed to the identification of material that will have specific action in relation to these receptor sites with a view to identifying compounds that can be used to control various  
15 disorders resulting from central nervous malfunction such as involuntary muscular activity and mental, affective or memory disorders. The compounds might also be used to control the perception of the sensation of pain.

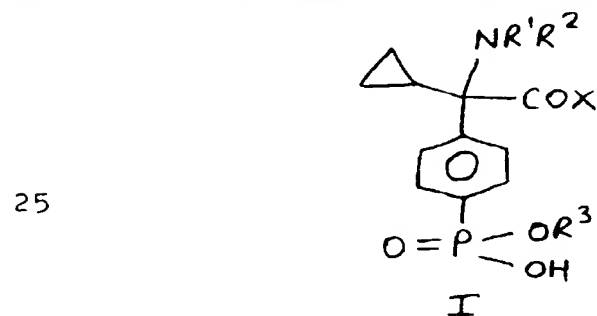
20 It is known that certain aryl compounds derived from 2-amino-2-phenylacetic acid (phenylglycine) bearing hydroxy and/or carboxy substituents in the phenyl ring and an alkyl or substituted alkyl or aryl substituent in the 2-position of the acetic acid moiety have actions at  
25 certain amino acid receptor sites in the CNS which are involved in the control of the transmission of nerve impulses in the brain and spinal cord, including those underlying memory processes and the perception of pain.

Compounds having activity at receptor sites in the CNS are disclosed  
30 WO 95/15941. This document discloses a large group of aryl substituted amino acids but specific mention is made of only one compound containing a cyclopropyl group i.e., 2-cyclopropyl-2-(4-carboxyphenyl) glycine. The compounds are described as having activity at metabotropic glutamate  
35 receptors (mGluRs).

To date molecular biologists have discovered eight sub-types of metabotropic glutamate receptor (mGluR) which have been divided into three main sub groups according to their sequence homology, signal transduction mechanism and their agonist selectivity. Sub group I mGluRs  
 5 consist of mGluR 1 and 5 and are selectively activated by (1S, 3R)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD). Sub group II mGluRs consist of mGluR 2 and 3 and are selectively activated by (1S, 3S)-ACPD. Sub group III mGluRs consist of mGluRs 4, 6, 7 and 8 and are potently  
 10 activated by L-2-amino-4-phosphonobutanoate (L-AP4).

It has now been found that a group of  $\alpha$ -cyclopropyl substituted phenylglycine compounds has unexpectedly improved pharmacological properties over those previously disclosed, for example, in WO 95/15941.  
 15 These advantages include greatly enhanced potency in their activity at mGluRs and higher selectivity for this type of receptor. The compounds are also selective for certain groups of mGluR. Specifically, the compounds act as potent and selective sub group III mGluR antagonists.

20 Accordingly, the present invention provides compounds of formula I



wherein:  $R^1$  and  $R^2$  are independently selected from hydrogen, optionally substituted alkyl and optionally substituted acyl;

30  $R^3$  is hydrogen or an optionally substituted group selected from alkyl, aryl and aralkyl; and

$X$  is  $OR^6$ , where  $R^6$  is hydrogen or optionally substituted alkyl, or  $NR^4R^5$ , where  $R^4$  and  $R^5$  are independently selected from hydrogen  
 35 and optionally substituted alkyl,

optionally substituted on the phenyl ring  
and pharmaceutically acceptable salts thereof.

The term "alkyl", as used herein, covers both straight chain and  
branched alkyl groups which have from 1 to 6 carbon atoms such as  
5 methyl, ethyl, propyl and butyl. An analagous convention applies to the  
term "acyl".

The alkyl and acyl groups in the compounds of the invention are  
optionally substituted by one or more groups selected from halogen,  
10 hydroxy, amino, carboxy, oxo, phosphono,  $-\text{PO}_2\text{H}(\text{OR}^7)$ , phosphinico,  $-\text{PO}_2\text{H}(\text{R}^7)$ ,  $-\text{OPO}_3\text{H}_2$ ,  $-\text{OPO}_2\text{H}(\text{OR}^7)$ , arsono,  $-\text{AsO}_2\text{H}(\text{OR}^7)$ , arsinico,  $-\text{AsO}_2\text{H}(\text{R}^7)$ , tetrazolyl, sulpho, sulphino, sulpheno, nitro, cyano, thio,  $-\text{OSO}_3\text{H}$ , aryl, and further optionally substituted alkyl or acyl groups.  $\text{R}^7$  is  
15 hydrogen or alkyl.

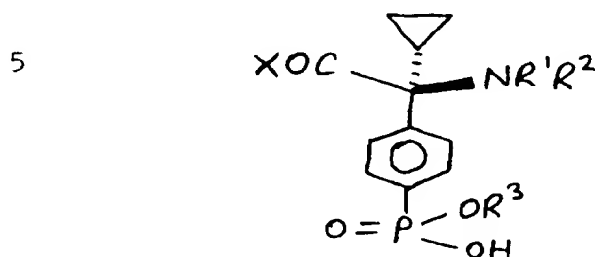
The term "aryl", as used herein, includes phenyl and naphthyl, each  
optionally substituted with up to five, preferably up to three, groups  
selected from halogen, nitro, cyano, alkyl, acyl, hydroxy, carboxy, amino,  
20 phenyl, alkylcarbonyloxy, alkoxycarbonyl, formyl or alkylcarbonyl. The term  
"aralkyl" refers to an alkyl group substituted with an aryl group such as  
optionally substituted benzyl.

The phenyl ring in the compounds of the invention may be  
25 substituted by from one to four groups selected from halogen, hydroxy,  
amino, carboxy, phosphono,  $-\text{PO}_2\text{H}(\text{OR}^7)$ , phosphinico,  $-\text{PO}_2\text{H}(\text{R}^7)$ ,  $-\text{OPO}_3\text{H}_2$ ,  $-\text{OPO}_2\text{H}(\text{OR}^7)$ , arsono,  $-\text{AsO}_2\text{H}(\text{OR}^7)$ , arsinico,  $-\text{AsO}_2\text{H}(\text{R}^7)$ , tetrazolyl, sulpho,  
sulphino, sulpheno, nitro, cyano, thio,  $-\text{OSO}_3\text{H}$  and optionally substituted  
30 alkyl, acyl or aryl. Substitution by halogen (especially chlorine) is preferred,  
particularly at the 3-position of the aromatic ring.

When used herein, the term "halogen" refers to fluorine, chlorine,  
bromine or iodine and an analagous convention applies to the term "halide".

The compounds of the invention have an asymmetric carbon atom  
35 bound to the phenyl ring and the invention includes racemic mixtures and

the individual stereoisomers. Preferably, the compound of formula I has the following stereochemistry at the carbon atom bound to the phenyl ring:



These enantiomers, conventionally designated as having S configuration, have been found to be particularly selective in their activity at mGluRs.

So far as the compounds of the invention contain other asymmetric centres, by virtue of optional substituents, the invention covers both optically active forms and racemic mixtures.

The compounds may take the form of the free compound as indicated in formula I or they may be in the form of their pharmaceutically acceptable salts. For example, the salts may be physiologically acceptable acid addition salts of a basic amino group in the molecule such as salts with hydrochloric acid, acetic acid, succinic acid, tartaric acid or citric acid. Salts may also be formed with an acidic group in the molecule, such as a carboxy or phosphono group, and suitable examples of this type of salt are mono-, di- and poly- sodium salts. When the compounds of the invention contain both basic and acidic groups, either or both of the basic and acidic groups can be present as salts.

The present invention includes compounds which are hydrolysable in vivo to compounds of formula I, such as the esters or amides of optional substituents.

Formula (I) includes solvates of the compound, such as with solvents used for purification of the compound e.g., by crystallisation.

Preferably  $R^1$  and  $R^2$  are both hydrogen. Suitably, X is OH.  $R^3$  is conveniently hydrogen.

A particularly preferred compound of the invention is 2-amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid and its pharmaceutically acceptable salts. Also preferred is 2-amino-2-cyclopropyl-2-(3-chloro-4-phosphonophenyl)acetic acid and its pharmaceutically acceptable salts.

The present invention also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable diluent or carrier. The use of the compounds for the treatment of a disorder of the CNS which comprises the administration to a patient of a pharmacologically effective amount of a compound or the composition of the invention is also contemplated, as is the use of the compounds in the manufacture of a medicament for the treatment of disorders of the CNS.

As a result of their activity as selective antagonists at mGluRs, the compounds of the invention depress nociceptive responses and may be used as analgesics. They may also be used in the treatment of other disorders of the CNS by utilisation of their selective antagonist activity at mGluRs, particularly sub group III mGluRs.

The compounds and compositions of the invention may be administered parenterally or orally, for example, intravenously for acute treatment or subcutaneously or orally for chronic treatment. The compounds may be formulated for clinical use in suitable vehicles, normally as a preparation of a water-soluble salt, though preparations of low water solubility, possibly in association with physiologically tolerable emulsifying agents, may be used for depot administration.

Since it is believed to be necessary for compounds of the invention to penetrate the blood brain barrier, it is frequently necessary to administer the compounds of the present invention in amounts significantly in excess of the amounts necessary to be achieved within the brain for the therapeutic effect desired and this will influence the concentration of the active

compounds in the composition of the present invention. Considerations of this type suggest that such a conventional dosage volume would provide the subject with up to about 200 mg/kg body weight although, when the compounds are to be administered by the intravenous route, dosages in the  
5 region of about 1-20 mg/kg body weight are to be expected for the more active compounds and/or for those substances with a high lipophilic or hydrophilic balance.

The compounds of the invention are also useful as research tools for  
10 investigating mechanisms of CNS activity. Thus, they may be used as radioactive ligands for receptor binding and metabolic studies. Formula I therefore includes radiolabelled compounds. Suitable radiolabelling includes, for example, the incorporation of an atom of a radioisotope such as tritium  
15 or iodine-125 into the compounds.

The compounds of the invention will also be useful for the isolation of receptors from central nervous tissue by, for example, linking the molecules via a spacer molecular chain to an affinity chromatography  
20 support material of the sepharose or agarose type.

The compounds of the invention may be prepared by methods well-known in the art, particularly by employing known methods of amino acid synthesis. Suitable synthetic methods are disclosed in WO 95/15941, for  
25 example, and include reactions involving the Strecker synthesis and the Bucherer-Berg synthesis. Hence, the compounds can be prepared by the reaction of the corresponding phenyl cyclopropyl ketone with an ammonium salt and a cyanide salt (e.g., ammonium carbonate, ammonium chloride and  
30 potassium cyanide) to convert the ketone group into an amino acid, followed, if necessary, by forming or adding the desired phosphono substituent at the 4- position on the phenyl ring.

Compounds of formula I which are substantially one optical isomer or are enriched in a particular optical isomer may be prepared by known  
35 stereoselective synthetic methods such as the established routes for



preparing amino acids using chiral reagents. Alternatively, optically active samples of the compounds can be prepared from the corresponding racemic mixtures by classical resolution procedures e.g., fractional crystallisation of the salt formed with R or S lysine or arginine, as appropriate.

5 The compounds may be purified using known chromatography techniques and/or by recrystallisation from a suitable solvent or mixture of solvents.

## 10 EXAMPLES

### EXAMPLE 1

#### (RS)-2-Amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid

15

##### (i) Synthesis

To a stirred mixture of 4-chlorophenyl cyclopropyl ketone (10g, 55.4 mmol) was added triethyl phosphite (2 ml) and anhydrous nickel chloride  
20 (0.73g) at 180-210°C for 3h. The mixture was cooled to room temperature and poured into water (100 ml). The resulting mixture was extracted with ethyl acetate (3 x 150 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The yield of crude  
25 cyclopropyl 4-(diethoxyphosphinyl)phenyl ketone was essentially quantitative.

Crude cyclopropyl 4-(diethoxyphosphinyl) phenyl ketone (15.6g, 55.4 mmol), ammonium carbonate (53.2g, 554 mmol), ammonium chloride  
30 (5.9g, 110 mmol) and potassium cyanide (18g, 277 mmol) in methanol (50 ml) and water (50 ml) were stirred at 65°C for 72h.

The mixture was then boiled in an open flask to eliminate excess ammonium carbonate. Concentrated HCl (100 ml) was carefully added and

35

the resulting mixture heated under reflux for 24h. Next day, the solution was evaporated under reduced pressure, the residue dissolved in a minimum amount of water and applied to a bed of AG50 H<sup>+</sup> ion-exchange resin. The column was eluted with water and then 1.0 M aqueous pyridine. The  
5 ninhydrin positive fractions of the 1.0 M aqueous pyridine eluate were combined and evaporated. The residue was dissolved in a minimum amount of water and applied to a bed of Dowex AG1 acetate ion-exchange resin. The column was eluted with water and then a gradient of aqueous  
10 acetic acid. Ninhydrin-positive fractions of the aqueous acetic acid eluate containing the desired compound were combined and evaporated. The residue was crystallized from ethanol/water. It gave (RS)-2-amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid, (540 mg) as a white solid.

15  
270 MHz <sup>1</sup>H nmr (D<sub>2</sub>O/NaOD, standard Me<sub>3</sub>Si(CH<sub>2</sub>)<sub>3</sub>SO<sub>3</sub>Na): δ 0.3-0.74 (m, 4H), 1.57 (m, 1H), 7.51 (m, 2H), 7.65 (m, 2H); 300 MHz <sup>13</sup>C nmr (D<sub>2</sub>O/NaOD, standard Me<sub>3</sub>Si(CH<sub>2</sub>)<sub>3</sub>SO<sub>3</sub>Na): δ 2.65, 3.78, 20.73, 66.65,  
20 128.25, 128.41, 132.68, 132.79, 142.98, 148.88, 185.29.

For C<sub>11</sub>H<sub>14</sub>NO<sub>5</sub>P.O.25H<sub>2</sub>O

Calculated C, 47.92; H, 5.30; N, 5.08%

25

Found C, 47.70; H, 5.61; N, 4.84%

#### (ii) Pharmacological Data

30

Table 1 shows antagonism by α-substituted-phenylglycines of L-AP4- and (1S, 3S)-ACPD- induced depression of dorsal root-evoked monosynaptic excitation of neonatal rat motoneurons.

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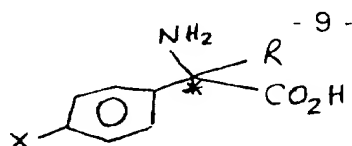


Table 1

Compound	R	X	Stereochemistry (*)	Apparent KD ( $\mu$ M) versus	
				L-AP4	(1S,3S)-ACPD
CPPG		PO <sub>3</sub> H <sub>2</sub>	RS	2.5 $\pm$ 0.3	51 $\pm$ 3
MCPG <sup>1</sup>	Me	CO <sub>2</sub> H	S	227 $\pm$ 12	9 $\pm$ 37
MPPG <sup>2</sup>	Me	PO <sub>3</sub> H <sub>2</sub>	RS	9.2 $\pm$ 0.3	113 $\pm$ 13
MTPG <sup>2</sup>	Me	Tetrazole	RS	188 $\pm$ 9	77.2 $\pm$ 7

<sup>1</sup> Values taken from Kemp et al (1994) Eur.J.Pharmacol-Molec.Pharmacol.Sect. 266 187-192

<sup>2</sup> Values taken from Jane et al (1995) Neuropharmacology 34 851-856

The pharmacological data show the enhanced potency of the compound and the greater selectivity for sub group III mGluRs over sub group II mGluRs. The compound is over three times as potent and more selective by a factor of about two, than the closely related  $\alpha$ -methyl substituted compound. In one aspect, therefore, the invention can be seen to be based on the selection of 2-amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid and analogous compounds from the broad disclosure in the prior art.

Table 2

Compound	IC <sub>50</sub> (nM) for reversal of inhibition of forskolin-stimulated cyclic AMP accumulation in adult rat cortical slices mediated by:	
	L-AP4 (10 $\mu$ m)	L-CCG-I (300 nM)
MPPG <sup>3</sup>	156 $\pm$ 29	69.5 $\pm$ 0.5
CPPG <sup>4</sup>	2.2 $\pm$ 0.6	46.2 $\pm$ 18.2

<sup>3</sup> Taken from Bedingfield et al., Eur. J. Pharmacol., 1996, 309, 71-78

<sup>4</sup> Taken from Toms et al., Br. J. Pharmacol., 1996, 119, 851-854

5 Table 2 shows antagonism by (RS)-MPPG and (RS)-CPPG of L-AP4- and L-CCG-I- induced inhibition of forskolin stimulated cyclic AMP accumulation in adult rat cortical slices. This data also shows the enhanced potency and greater selectivity of CPPG over previously reported compounds for subgroup III mGluRs (activated by L-AP4) over subgroup II mGluRs  
10 (activated by L-CCG-I). In this analysis, CPPG is more than 70 times more potent and also more selective for subgroup III mGluRs than the closely related  $\alpha$ -methyl compound.

## 15 EXAMPLE 2

### (RS)-2-Amino-2-cyclopropyl-2-(3-chloro-4-phosphonophenyl) acetic acid

A mixture of cyclopropyl (3-chloro-4-diethoxyphosphinylphenyl)  
20 ketone (7.86 g 24.8 mmol), potassium cyanide (8.06 g, 124 mmol), ammonium carbonate (23.8 g, 248 mmol) and ammonium chloride (2.65 g, 49.6 mmol) in 50% ethanol (200 ml) was heated to 60°C overnight. Next day, the mixture was cooled and evaporated and 6N aqueous hydrochloric  
25 acid (400 ml) was added to the residue. The mixture was heated under reflux overnight. Next day, the mixture was cooled, extracted with ethyl acetate (3 x 200 ml) and the aqueous layer evaporated under reduced pressure. The residue was dissolved in water and applied to a Dowex  
30 50WX8-400<sup>R</sup> (H<sup>+</sup> form) ion-exchange resin column (1L). The column was eluted with water until the eluate had a pH of about 5 and then elution was continued with 2M aqueous ammonia. Ninhydrin positive fractions of the aqueous ammonia eluate were combined and evaporated. The residue was  
35 dissolved in water and applied to a Dowex 1X8-400<sup>R</sup> (acetate form) ion-exchange resin column (100 ml). The column was eluted with water and

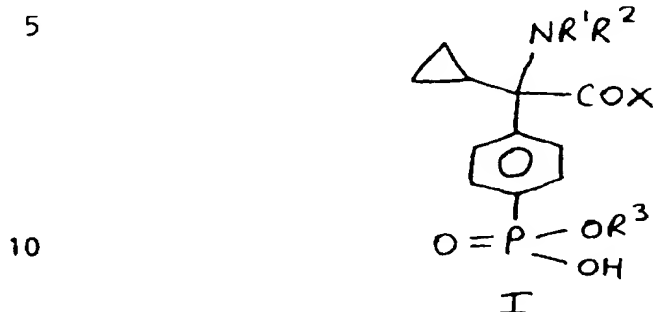
then successively with 0.1N, 0.5N, 1.0N, 2.0N, 3.0N and 4.0N aqueous acetic acid (500 ml of each). Ninhydrin positive fractions of the 4.0N aqueous acetic acid eluate were combined and evaporated. The resulting solid was crystallised from ethanol/water to give the title compound (130 mg) as a white solid.

300 MHz  $^1\text{H}$  nmr ( $\text{D}_2\text{O}$ , NaOD,  $\text{Me}_3\text{Si}(\text{CH}_2)_3\text{SO}_3\text{Na}$  as standard):  $\delta$  7.94 (1H, m), 7.77 (1H, m), 7.55 (1H, m), 1.65 (1H, m), 0.75 (3H, m) and 0.5 (1H, m).

Paper electrophoresis (pH4 buffer, 4 Kv): mobility relative to glutamic acid = 1.4.  $R_f$  = 0.5 (Silica gel coated tlc plates, eluent: (pyridine (3):acetic acid (8):water (11)): n-butanol 3:2)

CLAIMS

1. Compound of formula I

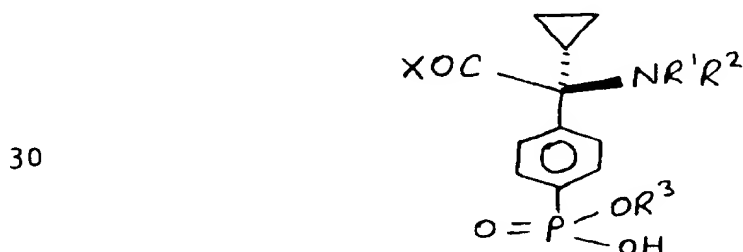


wherein:  $R^1$  and  $R^2$  are independently selected from hydrogen, optionally substituted alkyl and optionally substituted acyl;

15  $R^3$  is hydrogen or an optionally substituted group selected from alkyl, aryl and aralkyl; and

$X$  is  $OR^6$ , where  $R^6$  is hydrogen or optionally substituted alkyl, or  $NR^4R^5$ , where  $R^4$  and  $R^5$  are independently selected from hydrogen and optionally substituted alkyl, optionally substituted on the phenyl ring and pharmaceutically acceptable salts thereof.

25 2. Compound as claimed in claim 1 which has the following stereochemistry



3. Compound as claimed in claim 1 or claim 2, wherein  $R^1$  and  $R^2$  are both hydrogen.

35

4. Compound as claimed in any one of claims 1 to 3, wherein X is OH.
5. Compound as claimed in any one of claims 1 to 4, wherein R<sup>3</sup> is hydrogen.
- 5
6. Compound as claimed in any one of claims 1 to 5, wherein the phenyl ring has a chlorine atom substituted at the 3-position.
- 10
7. Compound as claimed in claim 1 which is 2-amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid or a pharmaceutically acceptable salt thereof.
8. Compound as claimed in claim 1 which is 2-amino-2-cyclopropyl-2-(3-chloro-4-phosphonophenyl) acetic acid or a pharmaceutically acceptable salt thereof.
- 15
9. Pharmaceutical composition comprising a compound of any one of claims 1 to 8 together with a pharmaceutically acceptable diluent or carrier.
- 20

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## INTERNATIONAL SEARCH REPORT

International Application No  
1/GB 96/03073A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07F9/38 A61K31/66 C07F9/40

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 15941 A (UNIVERSITY OF BRISTOL) 15 June 1995 cited in the application see particularly page 24, compound 34 ---	1-9
Y	EP 0 318 935 A (WARNER-LAMBERT CO.) 7 June 1989 see the whole document --- -/--	1-9

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

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Date of the actual completion of the international search

12 March 1997

Date of mailing of the international search report

20-03-1997

Name and mailing address of the ISA

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Authorized officer

Beslier, L



# INTERNATIONAL SEARCH REPORT

International Application No.

PC./GB 96/03073

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>BR. J. PHARMACOL. (BJPCBM,00071188);96;  VOL.119 (5); PP.851-854,  - 21 October 1996 UNIVERSITY OF  BRISTOL;DEPARTMENT OF PHARMACOLOGY;  BRISTOL; BS8 1TD; UK (GB), XP000618728  TOMS N J ET AL: "The effects of  (RS)-.alpha.-cyclopropyl-4-phosphonophenyl  glycine ((RS)-CPPG), a potent and  selective metabotropic glutamate receptor  antagonist"  see the whole document  -----</p>	1-9

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

/GB 96/03073

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9515941 A	15-06-95	AU 1246895 A EP 0733037 A	27-06-95 25-09-96
EP 318935 A	07-06-89	US 5175153 A AT 118009 T DE 3852935 D DE 3852935 T ES 2068194 T JP 1230590 A	29-12-92 15-02-95 16-03-95 24-05-95 16-04-95 14-09-89

Form PCT/ISA/210 (patent family annex) (July 1992)

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> C07C 229/28, 229/46, A61K 31/195, C07D 233/78, C07F 9/38, C07D 335/12, C07F 5/02, C07C 309/27	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/54280</b> <b>(43) International Publication Date:</b> 28 October 1999 (28.10.99)
<b>(21) International Application Number:</b> PCT/CA99/00311 <b>(22) International Filing Date:</b> 19 April 1999 (19.04.99) <b>(30) Priority Data:</b> 2,235,119 17 April 1998 (17.04.98) CA <b>(71)(72) Applicants and Inventors:</b> <del>ECURRY</del> , Kenneth [CA/CA]; 1176 East King Edward Avenue, Vancouver, British Colum- bia V5V 2G2 (CA); <del>PAJOUHESH</del> , Hassan [IR/CA]; Suite 601, 1020 Harwood Street, Vancouver, British Columbia V6E 1S1 (CA). <b>(74) Agent:</b> MBM & CO.; P.O. Box 809, Station B, Ottawa, Ontario K1P 5P9 (CA).	<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(54) Title:</b> CUBANE DERIVATIVES AS METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS AND PROCESS FOR THEIR PREPARATION		
<b>(57) Abstract</b>  The present invention relates to therapeutically active cubane compounds, a method of preparing the same, and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in treating diseases of the central nervous system related to the metabotropic glutamate receptor system.		



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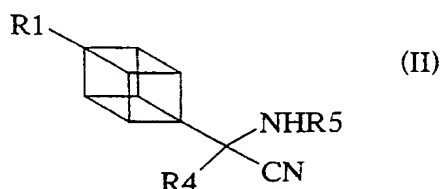


## AMENDED CLAIMS

[received by the International Bureau on 28 October 1999 (28.10.99);  
original claims 3 and 4 amended; remaining claims unchanged (1 page)]

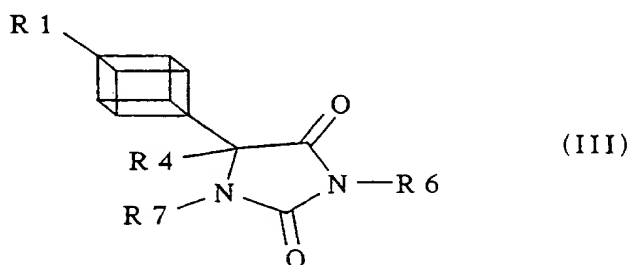
3. A compound as claimed in claim 1, wherein **R2** is  $\text{NH}_2$ .
4. A compound as claimed in claim 1, wherein **R3** can be -H, or -Me; or xanthyl or thioxanthyl and **R4** is  $\text{COOH}$ .
5. A process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolyzing a compound of formula:



in which **R1** is defined as above, **R5** represents a hydrogen atom or an acyl group and **R4** has the meaning defined above. Preferred values for **R5** are hydrogen and (2-6C) alkanoyl groups, such as acetyl;

(b) hydrolyzing a compound of formula:



wherein **R6** and **R7** each independently represent a hydrogen atom, a (2-6C) alkanoyl

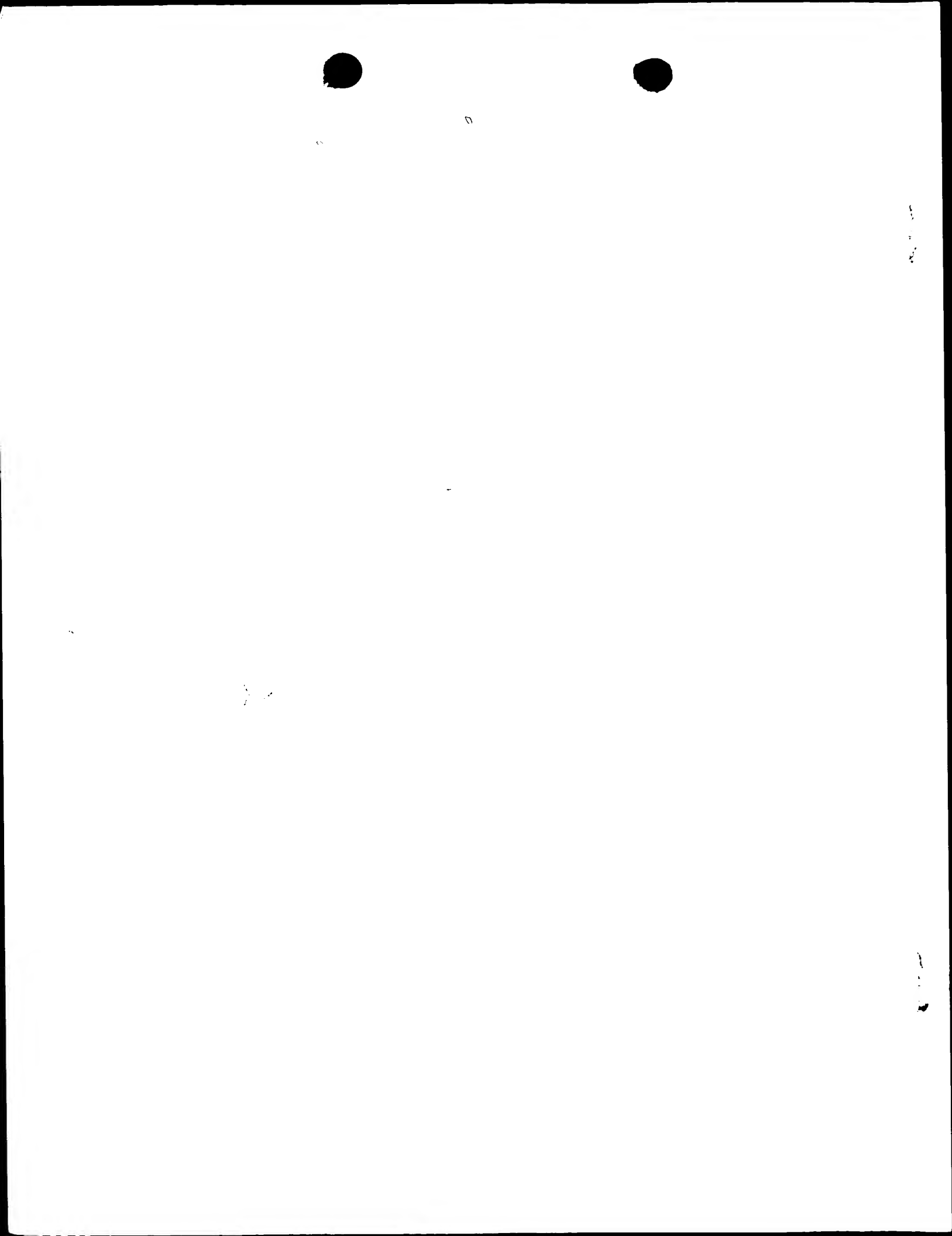




## STATEMENT UNDER ARTICLE 19

Claim 3 has been amended to read "...wherein R2 is NH<sub>2</sub>." and claim 4 has been amended to read "...and R4 is COOH." These amendments are made to correct a typographical error. The fact that the error was merely typographical can be determined from multiple descriptions throughout the patent application that are consistent with the assignment that R2 is NH<sub>2</sub> in claim 3, and that R4 is COOH for claim 4. For example, claim 1, which is also included within the summary of the invention, states that **R2** can be a **basic group** selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea, and that **R4** can be an **acidic group** selected from the group consisting of **carboxyl**, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol. Thus, the assignment of R2 and R4 within the dependent claims must be consistent with the categories delineated in claim 1. Moreover, schematics of the synthetic procedures presented on pages 30 and 32 (Examples I and II, respectively), support the interpretation that **R2** is NH<sub>2</sub> and **R4** is COOH, and that the interchange of assignment between the two was merely typographical in nature.

The applicant notes that the International Searching Authority has only searched claims 2 through 10. While the applicant asserts that the Searching Authority should be searching claim 1, it accepts that the written opinion may be directed to claims 2 through 10 only.



**CUBANE DERIVATIVES AS METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS AND PROCESS FOR THEIR PREPARATION****FIELD OF THE INVENTION**

This invention pertains to therapeutically active cubane derivatives, a method for preparing the same, pharmaceutical compositions comprising the compounds and a method of treating diseases of the Central Nervous System (CNS) therewith.

**BACKGROUND OF THE INVENTION**

The acidic amino acid L-Glutamate is recognized as the major excitatory neurotransmitter in the CNS. The receptors that respond to L-Glutamate are called excitatory amino acid receptors. The excitatory amino acid receptors are thus of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiratory and cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types and both are activated by L-Glutamic acid and its analogs. Receptors activated by L-Glutamic acid that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic." This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists N-Methyl-D-aspartate (NMDA),  $\alpha$ -Amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and Kainic acid (KA).

The second general type of receptor is the G-protein or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D, increases or decreases in cAMP formation, and changes in ion channel function (Schoepp and Conn, *Trends in Pharmacological Science*, 14:13, 1993). Both types of receptors appear not only to mediate normal synaptic transmission along excitatory pathways but also to participate in the modification of synaptic connections during development and throughout life.

So far eight different clones of the G-protein-coupled metabotropic glutamate receptors (mGluRs) have been identified (Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426). These receptors function to modulate the presynaptic release of L-Glutamate, and the postsynaptic



sensitivity of the neuronal cell to L-Glutamate excitation. Based on pharmacology, sequence homology and the signal transduction pathway that they activate, the mGluRs have been subclassified into three groups. The mGluR<sub>1</sub> and mGluR<sub>5</sub> receptors form group I. They are coupled to hydrolysis of phosphatidylinositol (PI) and are selectively activated by (*RS*)-3,5-dihydroxyphenylglycine (Brabet et al., *Neuropharmacology*, 34, 895-903, 1995). Group II comprises mGluR<sub>2</sub> and mGluR<sub>3</sub> receptors. They are negatively coupled to adenylate cyclase and are selectively activated by (2*S*,1'*R*,2'*R*,3'*R*)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV; Hayashi et al., *Nature*, 366, 687-690, 1993). Finally, the mGluR<sub>4</sub>, mGluR<sub>6</sub>, mGluR<sub>7</sub> and mGluR<sub>8</sub> receptors belong to group III. They are also negatively coupled to adenylate cyclase and are selectively activated by (L)-2-amino-4-phosphonobutyric acid (L-AP4; Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426).

Agonists and antagonists of these receptors are believed useful for the treatment of acute and chronic neurodegenerative conditions, and as antipsychotic, anticonvulsant, analgesic, anxiolytic, antidepressant, and anti-emetic agents. Antagonists and agonists of neural receptors are classified as selective for a particular receptor or receptor subtype, or as non-selective. Antagonists may also be classified as competitive or non-competitive. While competitive and non-competitive antagonists act on the receptors in a different manner to produce similar results, selectivity is based upon the observations that some antagonists exhibit high levels of activity at a single receptor type, and little or no activity at other receptors. In the case of receptor-specific diseases and conditions, the selective agonists and antagonists are of the most value.

Compounds such as L-Glutamic acid, Quisqualic acid and Ibotenic acid are known to act as non-selective agonists on the mGluRs, while selective ionotropic glutamate receptor agonists such as NMDA, AMPA and Kainic acid have little effect on these receptors. Recently a few compounds without activity at the ionotropic glutamate receptors but with activity at the metabotropic receptors have been identified. These include *trans*-ACPD (*trans* (1*S*,3*R*-1-aminocyclopentane-1,3-dicarboxylic acid), the partial agonist L-AP3 (L-2-amino-3-phosphonopropionic acid; Palmer, E., Monaghan, D. T. and Cotman, C. W. *Eur. J. Pharmacol.* 166, 585-587, 1989; Desai, M. A. and Conn, P. J. *Neuroscience Lett.* 109, 157-162, 1990; Schoepp, D. D. et al., *J. Neurochemistry*. 56, 1789-1796, 1991; Schoepp D. D. and Johnson B. G. *J. Neurochemistry* 53, 1865-1613, 1989), L-AP4 (L-2-amino-4-phosphonobutyric acid) which is an agonist at the mGluR<sub>4</sub> receptor (Thomsen C. et al., *Eur. J. Pharmacol.* 227, 361-362, 1992) and some of the isomers of CCG (2-(carboxycyclopropyl)glycines) especially L-CCG-I and L-CCG-II (Hayashi, Y. et al., *Br. J. Pharmacol.* 107, 539-543, 1992).



Very few selective antagonists at the mGluRs have been reported. However some phenylglycine derivatives, *S*-4CPG (*S*-4-carboxyphenylglycine), *S*-4C3HPG (*S*-4-carboxy -3-hydroxyphenylglycine) and *S*-MCPG (*S*- $\alpha$ -methyl-4-carboxyphenylglycine) have been reported to antagonize *trans*-ACPD- stimulated phosphoinositide hydrolysis and thus possibly act as antagonists at mGluR<sub>1</sub> and mGluR<sub>5</sub> subtypes (Thomsen, C. and Suzdak, P, *Eur. J. Pharmacol.* 245, 299, 1993).

Research directed towards mGluRs is beginning to show that mGluRs may be implicated in a number of normal as well as pathological mechanisms in the brain and spinal cord. For example, activation of these receptors on neurons can: influence levels of alertness, attention and cognition; protect nerve cells from excitotoxic damage resulting from ischemia, hypoglycemia and anoxia; modulate the level of neuronal excitation; influence central mechanisms involved in controlling movement; reduce sensitivity to pain; reduce levels of anxiety.

The use of compounds active at the mGluRs for the treatment of epilepsy is corroborated by investigations of the influence of *trans*-ACPD on the formation of convulsions (Sacaan and Schoepp, *Neuroscience Lett.* 139, 77, 1992) and that phosphoinositide hydrolysis mediated via mGluR is increased after kindling experiments in rats (Akiyama et al. *Brain Res.* 569, 71, 1992).

*Trans*-ACPD has been shown to increase release of dopamine in the rat brain, which indicates that compounds acting on the mGluRs might be usable for the treatment of Parkinson's disease and Huntington's Chorea (Sacaan et al., *J. Neurochemistry* 59, 245, 1992).

*Trans*-ACPD has also been shown to be a neuroprotective agent in a medial cerebral artery occlusion (MCAO) model in mice (Chiamulera et al. *Eur. J. Pharmacol.* 215, 353, 1992), and it has been shown to inhibit NMDA-induced neurotoxicity in nerve cell cultures (Koh et al., *Proc. Natl. Acad. Sci. USA* 88, 9431, 1991). The mGluR-active compounds are also implicated in the treatment of pain. This is proved by the fact that antagonists at the metabotropic glutamate receptors antagonize sensory synaptic response to noxious stimuli of thalamic neurons (Eaton, S. A. et al., *Eur. J. Neuroscience*, 5, 186, 1993).

The use of compounds active at the mGluRs for treatment of neurological diseases such as senile dementia have also been indicated by the findings of Zheng and Gallagher (*Neuron* 9, 163, 1992) and Bashir et al. (*Nature* 363, 347, 1993) who demonstrated that activation of mGluRs is necessary for the induction of long-term potentiation (LTP) in nerve cells (septal nucleus, hippocampus) and the finding that long-term depression is induced after activation of metabotropic glutamate receptors in cerebellar granule cells (Linden et al. *Neuron* 7, 81, 1991).





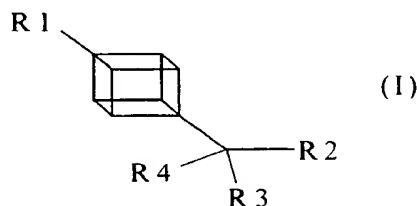
Thus compounds that demonstrate either activating or inhibiting activity at mGluRs have therapeutic potential for the treatment of neurological disorders. These compounds have application as new drugs to treat both acute and chronic neurological disorders, such as stroke and head injuries; epilepsy; movement disorders associated with Parkinson's disease and Huntington's chorea; pain; anxiety; AIDS dementia; and Alzheimer's disease. Since the mGluRs can influence levels of alertness, attention and cognition; protect nerve cells from excitotoxic damage resulting from ischemia, hypoglycemia and anoxia; modulate the level of neuronal excitation; influence central mechanisms involved in controlling movement; reduce sensitivity to pain; and reduce levels of anxiety, these compounds can also be used to influence these situations and also find use in learning and memory deficiencies such as senile dementia. mGluRs may also be involved in addictive behavior, alcoholism, drug addiction, sensitization and drug withdrawal (*Science*, 280:2045, 1998), so compounds acting at mGluRs might also be used to treat these disorders.

The current pharmaceutical options for treating neurological disorders tend to be very general and non-specific in their actions in that, although they may reduce the clinical symptoms associated with a specific neurological disorder, they may also negatively impact normal function of the central nervous system of patients. Thus new cellular targets and drugs that are more specific in their actions require to be identified and developed and thus a need remains for chemical compounds that demonstrate specific binding characteristics towards mGluRs.



## SUMMARY OF THE INVENTION

It is an object of this invention to provide novel compounds that demonstrate activity at the various metabotropic glutamate receptors (mGluRs). In particular, a compound of Formula I and stereoisomers thereof:



wherein:

**R<sub>1</sub>** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfino, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, -CH<sub>2</sub>-isoxazol and higher homologues thereof;

**R<sub>2</sub>** can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea;

**R<sub>3</sub>** can be H, aliphatic, aromatic or heterocyclic;

**R<sub>4</sub>** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol;

and pharmaceutically acceptable salts thereof.

## DETAILED DESCRIPTION OF THE INVENTION

The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius; "N" refers to normal or normality; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "mL" means milliliter or milliliters; "M" refers to molar or molarity; "MS" refers to mass spectrometry; "IR"



refers to infrared spectroscopy; and "NMR" refers to nuclear magnetic resonance spectroscopy.

As would be understood by the skilled artisan throughout the synthesis of the compounds of Formula I, it may be necessary to employ an amino-protecting group or a carboxy-protecting group in order to reversibly preserve a reactively susceptible amino or carboxy functionality while reacting other functional groups on the compound.

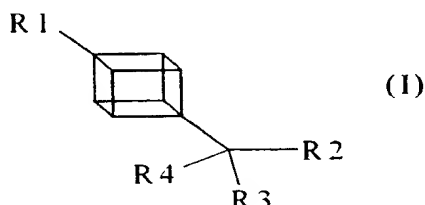
Examples of such amino-protecting groups include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, *t*-butoxycarbonyl, 2-(4-xenyl)-isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxy-carbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfono)-ethoxycarbonyl, 2-(methylsulfono)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; benzoylmethylsulfono group, 2-nitrophenylsulfenyl, diphenylphosphine oxide and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino-protecting group(s). Preferred amino-protecting groups are *t*-butoxycarbonyl (*t*-Boc), allyloxycarbonyl and benzyloxycarbonyl (CbZ). Further examples of these groups are found in E. Haslam in *Protective Groups in Organic Synthesis*; McOmie, J. G. W., Ed. 1973, at Chapter 2; and Greene, T.W. and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, Second edition; Wiley-Interscience: 1991; Chapter 7.

Examples of such carboxyl-protecting groups include methyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, *t*-butyl, *t*-amyl, trityl,



4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4''-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, *t*-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl,  $\beta$ -(di(*n*-butyl)methylsilyl)ethyl, *p*-toluenesulfonoethyl, 4-nitrobenzylsulfonoethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl and like moieties. Preferred carboxyl-protecting groups are allyl, benzyl and *t*-butyl. Further examples of these groups are found in E. Haslam, *supra*, at Chapter 5; and T. W. Greene and P. G. M. Wuts, *supra*, at Chapter 5.

The present invention provides a compound of the formula:



wherein:

**R<sup>1</sup>** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfinio, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, -CH<sub>2</sub>-isoxazol and higher analogues thereof;

**R<sup>2</sup>** can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea ;

**R<sup>3</sup>** can be H, aliphatic, aromatic or heterocyclic;

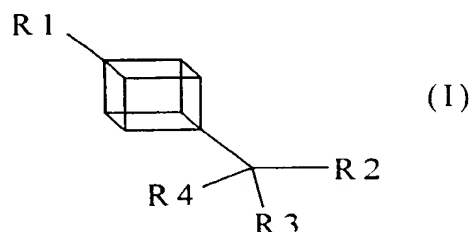
**R<sup>4</sup>** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol;

and pharmaceutically acceptable salts thereof.





In particular compounds wherein the compound of Formula I is selected from the group consisting of:



wherein:

**R1** is COOH

**R2** is COOH

**R3** can be H or methyl or xanthyl or thioxanthyl and

**R4** is NH<sub>2</sub>

While all of the compounds of Formula I are believed to demonstrate activity at the metabotropic glutamate receptors (mGluRs), certain groups of Formula I compounds are more preferred for such use.

As noted above, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic



acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen carries a suitable organic group such as an alkyl, alkenyl, alkynyl, or aralkyl moiety.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. This invention further encompasses the pharmaceutically acceptable solvates of the compounds of Formula I. Many of the Formula I compounds can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

The compounds of the present invention have multiple asymmetric (chiral) centers. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of



diastereomers. All asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

The prefixes "*R*" and "*S*" are used herein as commonly used in organic chemistry to denote the absolute configuration of a chiral center, according to the Cahn-Ingold-Prelog system. The stereochemical descriptor *R* (*rectus*) refers to that configuration of a chiral center with a clockwise relationship of groups tracing the path from highest to second-lowest priorities when viewed from the side opposite to that of the lowest priority group. The stereochemical descriptor *S* (*sinister*) refers to that configuration of a chiral center with a counterclockwise relationship of groups tracing the path from highest to second-lowest priority when viewed from the side opposite to the lowest priority group. The priority of groups is decided using sequence rules as described by Cahn et al., *Angew. Chem.*, 78, 413-447, 1966 and Prelog, V. and Helmchen, G.; *Angew. Chem. Int. Ed. Engl.*, 21, 567-583, 1982).

In addition to the *R,S* system used to designate the absolute configuration of a chiral center, the older D-L system is also used in this document to denote relative configuration, especially with reference to amino acids and amino acid derivatives. In this system a Fischer projection of the compound is oriented so that carbon-1 of the parent chain is at the top. The prefix "D" is used to represent the relative configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and "L", that of the isomer in which it is on the left.

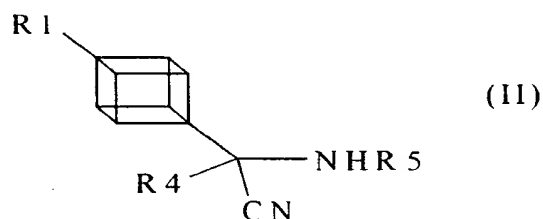
As would be expected, the stereochemistry of the Formula I compounds is critical to their potency as agonists or antagonists. The relative stereochemistry is established early during synthesis, which avoids subsequent stereoisomer separation problems later in the process. Further manipulation of the molecules then employs stereospecific procedures so as to maintain the preferred chirality. The preferred methods of this invention are the methods employing those preferred compounds.

Non-toxic metabolically-labile esters and amides of compounds of Formula I are ester or amide derivatives of compounds of Formula I that are hydrolyzed in vivo to afford said compounds of Formula I and a pharmaceutically acceptable alcohol or amine. Examples of metabolically-labile esters include esters formed with (1-6C) alkanols in which the alkanol moiety may be optionally substituted by a (1-8C) alkoxy group, for example methanol, ethanol, propanol and methoxyethanol. Examples of metabolically-labile amides include amides formed with amines such as methylamine.



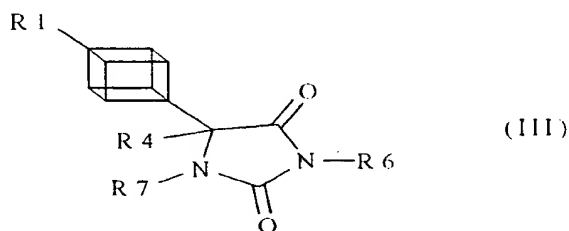
According to another aspect, the present invention provides a process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolyzing a compound of formula:



in which **R1** is defined as above, **R5** represents a hydrogen atom or an acyl group and **R4** has the meaning defined above. Preferred values for **R5** are hydrogen and (2-6C) alkanoyl groups, such as acetyl.

(b) hydrolyzing a compound of formula:

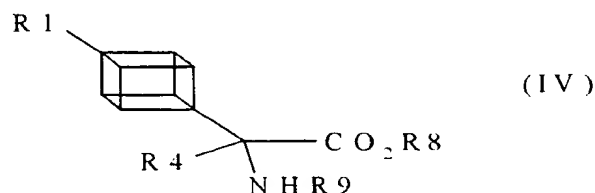


in which **R6** and **R7** each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof; or:





(c) deprotecting a compound of formula:



in which **R8** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R9** represents a hydrogen atom or a nitrogen protecting group;

whereafter, if necessary and/or desired:

- (i) resolving the compound of Formula I;
- (ii) converting the compound of Formula I into a non-toxic metabolically-labile ester or amide thereof;
- and/or;
- (iii) converting the compound of Formula I or a non-toxic metabolically-labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

The protection of carboxylic acid and amine groups is generally described in McOmie, *Protecting Groups in Organic Chemistry*, Plenum Press, NY, 1973, and Greene and Wuts, *Protecting Groups in Organic Synthesis*, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxyl protecting groups include alkyl groups such as methyl, ethyl, *t*-butyl and *t*-amyl; aralkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and *t*-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine-protecting groups include acyl groups, such as groups of formula **R9** CO in which **R9** represents (1-6C) alkyl, (3-10C) cycloalkyl, phenyl(1-6C) alkyl, phenyl(1-6C) alkoxy, or a (3-10C) cycloalkoxy, wherein a phenyl group may optionally be substituted by one or two



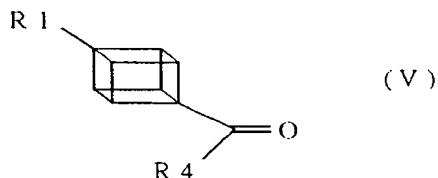
substituents independently selected from amino, hydroxy, nitro, halogeno, (1-6C) alkyl, (1-6C) alkoxy, carboxyl, (1-6C) alkoxycarbonyl, carbamoyl, (1-6C) alkanoylamino, (1-6C) alkylsulphonylamino, phenylsulphonylamino, toluenesulphonylamino, and (1-6C) fluoroalkyl.

The compounds of Formula II are conveniently hydrolyzed in the presence of an acid, such as hydrochloric acid or sulfuric acid, or a base, such as an alkali metal hydroxide, for example sodium hydroxide. The hydrolysis is conveniently performed in an aqueous solvent such as water and at a temperature in the range of 50 to 200 °C.

The compounds of Formula III are conveniently hydrolyzed in the presence of a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline earth metal hydroxide such as barium hydroxide. Suitable reaction media include water. The temperature is conveniently in the range of from 50 to 150 °C.

The compounds of Formula IV may be deprotected by a conventional method. Thus, an alkyl carboxyl protecting group may be removed by hydrolysis. The hydrolysis may conveniently be performed by heating the compound of Formula V in the presence of either a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline metal hydroxide, such as barium hydroxide, or an acid such as hydrochloric acid. The hydrolysis is conveniently performed at a temperature in the range from 10 to 300 °C. An aralkyl carboxyl protecting group may conveniently be removed by hydrogenolysis. The hydrogenolysis may conveniently be effected by reacting the compound of Formula V with hydrogen in the presence of a Group VIII metal catalyst, for example a palladium catalyst such as palladium on charcoal. Suitable solvents for the reaction include alcohols such as ethanol. The reaction is conveniently performed at a temperature in the range from 0 to 100 °C. An acyl, amine protecting group is also conveniently removed by hydrolysis, for example as described for the removal of an alkyl carboxyl protecting group.

The compounds of Formula II may be prepared by reacting a compound of formula:



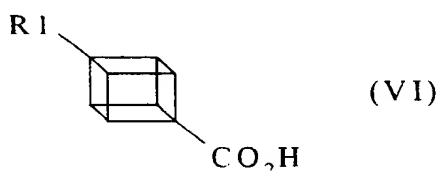


with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and an ammonium halide, such as ammonium chloride, conveniently in the presence of ultrasound. Thus, the ammonium halide is mixed with chromatography grade alumina in the presence of a suitable diluent such as acetonitrile. The mixture is then irradiated with ultrasound, whereafter the compound of Formula V is added, and the mixture is again irradiated. The alkali metal cyanide is then added, followed by further irradiation with ultrasound.

Individual isomers of compounds of Formula II may be made by reacting a compound of the Formula V with the stereoisomers of the chiral agent (*S*)- and (*R*)-phenylglycinol and a reactive cyanide such as trimethylsilyl cyanide.

The compounds of Formula III may be prepared by reacting a compound of Formula V with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and ammonium carbonate or ammonium carbamate. Convenient solvents include water, dilute ammonium hydroxide, alcohols such as methanol, aqueous methanol and aqueous ethanol. Conveniently the reaction is performed at a temperature in the range of from 10 to 150 °C. If desired, the compounds of Formula III may then be alkylated, for example using an appropriate compound of formula **R6** Cl and/or **R7** Cl.

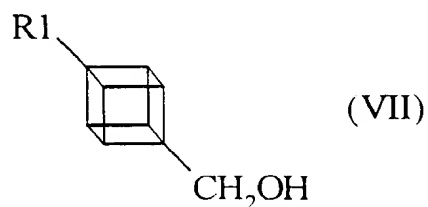
The compounds of Formula V can be prepared by reacting a compound of formula:



with a chlorinating agent such as thionyl chloride or phosphorous(V) chloride, followed by reaction with **R4X** wherein **R4** has the meaning defined above and **X** is halogen or OH.

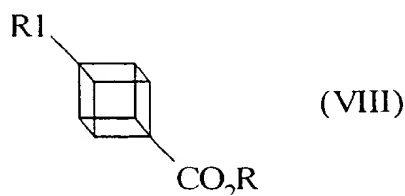


The compounds of Formula V can also be prepared by oxidizing a compound of formula



under Swern conditions.

The compounds of Formula VI can be prepared from compounds of formula:



by reduction.

If **R1** is CO<sub>2</sub>Me, this compound can be bought commercially. If **R1** is another substituent, the compound of Formula VIII can be made using standard procedures.

Many of the intermediates described herein, for example the compounds of Formula II, III and IV are believed to be novel, and are provided as further aspects of the invention.

The Formula I compounds of the present invention are agonists or antagonists at certain metabotropic excitatory amino acid receptors (mGluRs). Therefore, another aspect of the present invention is a method of affecting mGluRs in mammals, which comprises administering to a mammal requiring modulated excitatory amino acid neurotransmission a pharmacologically-effective amount of a compound of Formula I. The term "pharmacologically-effective amount" is used to represent an amount of the compound of the invention that is capable of affecting the mGluRs. By affecting, a compound of the invention is acting as an agonist or antagonist. When a compound of the





invention acts as an agonist, the interaction of the compound with the excitatory amino acid receptor mimics the response of the interaction of this receptor with its natural ligand (i.e. L-Glutamic acid). When a compound of the invention acts as an antagonist, the interaction of the compound with the excitatory amino acid receptor blocks the response of the interaction of this receptor with its natural ligand (i.e. L-Glutamic acid).

The particular dose of compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the compound may be administered by continuous infusion. A typical daily dose will contain from about 0.001 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 20 mg/kg.

A variety of physiological functions have been shown to be subject to influence by excessive or inappropriate stimulation of excitatory amino acid transmission. The Formula I compounds of the present invention are believed (through their interactions at the mGluRs) to have the ability to treat a variety of neurological disorders in mammals associated with this condition, including acute neurological disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia (e.g. stroke and cardiac arrest), spinal cord trauma, head trauma, perinatal hypoxia, and hypoglycemic neuronal damage. The Formula I compounds are believed to have the ability to treat a variety of chronic neurological disorders, such as Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage and retinopathy, cognitive disorders, and idiopathic and drug-induced Parkinson's disease. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of Formula I.

The Formula I compounds of the present invention (through their interactions at the mGluRs) are also believed to have the ability to treat a variety of other neurological disorders in mammals that are associated with glutamate dysfunction, including muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, anxiety and related disorders (e.g. panic attack), emesis, brain edema, chronic pain, sleep disorders, Tourette's syndrome, attention



deficit disorder, and tardive dyskinesia. Therefore, the present invention also provides methods for treating these disorders which comprise administering to a patient in need thereof an effective amount of the compound of Formula I.

The Formula I compounds of the present invention (through their interactions at the mGluRs) are also believed to have the ability to treat a variety of psychiatric disorders, such as schizophrenia, anxiety and related disorders (e.g. panic attack), depression, bipolar disorders, psychosis, and obsessive compulsive disorders. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of Formula I.

The pharmacological properties of the compounds of the invention can be illustrated by determining their effects in various functional in vitro assays. The compounds of the invention were studied in an in vitro assay that measured the inhibition of PI hydrolysis or the formation of cyclic AMP in Chinese hamster ovary cell lines expressing mGluR<sub>1a</sub>, mGluR<sub>2</sub> and mGluR<sub>4a</sub> cloned metabotropic glutamate receptors.

### ***Principle***

So far eight different clones of the G-protein-coupled mGluRs have been identified (Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426). These receptors function to modulate the presynaptic release of L-Glutamate, and the postsynaptic sensitivity of the neuronal cell to L-Glutamate excitation. Based on pharmacology, sequence homology and the signal transduction pathway that they activate, the mGluRs have been subclassified into three groups. The mGluR<sub>1</sub> and mGluR<sub>5</sub> receptors form group I. They are coupled to hydrolysis of phosphatidylinositol (PI) and are selectively activated by (*RS*)-3,5-dihydroxyphenylglycine (Brabet et al., *Neuropharmacology*, 34, 895-903, 1995). Group II comprises mGluR<sub>2</sub> and mGluR<sub>3</sub> receptors. They are negatively coupled to adenylate cyclase and are selectively activated by (2*S*,1'*R*,2'*R*,3'*R*)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV; Hayashi et al., *Nature*, 366, 687-690, 1993). Finally, the mGluR<sub>4</sub>, mGluR<sub>6</sub>, mGluR<sub>7</sub> and mGluR<sub>8</sub> receptors belong to group III. They are also negatively coupled to adenylate cyclase and are selectively activated by (*S*)-2-amino-4-phosphonylbutyric acid (L-AP4; Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426).



### Cell Culture

The Chinese hamster ovary cell lines expressing mGluR<sub>1a</sub>, mGluR<sub>2</sub> and mGluR<sub>4a</sub> receptors have been described previously (Aramori and Nakanishi, *Neuron* 8, 757-765; 1992; Tanabe et al., *Neuron* 8, 169-179, 1992; Tanabe et al., *J. Neurosci.* 13, 1372-1378). They were maintained at 37°C in a humidified 5% CO<sub>2</sub> incubator in Dulbecco's Modified Eagle Medium (DMEM) containing a reduced concentration of (S)-glutamine (2mM) and were supplemented with 1% proline, penicillin (100 U/ml), streptomycin (100 mg/ml) and 10% dialyzed fetal calf serum (all GIBCO, Paisley). Two days before assay  $1.8 \times 10^6$  cells were divided into the wells of 24 well plates.

### Second Messenger Assays

PI hydrolysis was measured as described previously (Hayashi et al., *Br. J. Pharmacol.* 107, 539-543, 1992; Hayashi et al., *J. Neurosci.* 14, 3370-3377, 1994). Briefly, the cells were labeled with [<sup>3</sup>H]inositol (2 µCi/ml) 24 h prior to the assay. For agonist assays, the cells were incubated with ligand dissolved in phosphate-buffered saline (PBS)-LiCl for 20 min, and agonist activity was determined by measurement of the level of <sup>3</sup>H-labeled mono-, bis- and tris-inositol phosphates by ion-exchange chromatography. For antagonist assays, the cells were preincubated with the ligand dissolved in PBS-LiCl for 20 min prior to incubation with ligand and 10 µM (L)-Glutamic acid for 20 min. The antagonist activity was then determined as the inhibitory effect of the (L)-Glutamic acid-mediated response. The assay of cyclic AMP formation was performed as described previously (Hayashi et al., *Br. J. Pharmacol.* 107, 539-543, 1992; Hayashi et al., *J. Neurosci.* 14, 3370-3377, 1994). Briefly, the cells were incubated for 10 min in PBS containing the ligand and 10 µM forskolin and 1mM 3-Isobutyl-1-methyloxanthine (IBMX; both Sigma, St. Louis, MO, USA). The agonist activity was then determined as the inhibitory effect of the forskolin-induced cyclic AMP formation. For antagonist assay, the cells were preincubated with ligand dissolved in PBS containing 1 mM IBMX for 20 min prior to a 10 min incubation in PBS containing the ligand, 20 µM (mGluR<sub>2</sub>) or 50 µM (mGluR<sub>4a</sub>), (L)-Glutamic acid, 10 µM Forskolin and 1 mM IBMX.

### Results

Some of the compounds of the invention were tested for antagonist activity against Chinese hamster



ovary cell lines expressing mGluR<sub>1α</sub>, mGluR<sub>2</sub> and mGluR<sub>4a</sub> cloned mGluRs at a concentration of 1 mM. When tested as antagonists of the increase in PI hydrolysis evoked by 10 μM (L)-Glutamic acid, some compounds of the invention effectively blocked this increase in PI hydrolysis by an action at the mGluR<sub>1α</sub> receptor. The data for one of the compounds of the invention is shown in Figure 1 below.

According to another aspect, the present invention provides a method of modulating one or more metabotropic glutamate receptor functions in a warm-blooded mammal which comprises administering an effective amount of a compound of Formula I, or a non-toxic metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof.

The compounds of the present invention are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical formulation comprising a compound of Formula I and a pharmaceutically-acceptable carrier, diluent, or excipient. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active ingredient.

The compounds of Formula I are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

The present invention also provides pharmaceutical compositions containing compounds as disclosed in the claims in combination with one or more pharmaceutically acceptable, inert or physiologically active, diluent or adjuvant. The compounds of the invention can be freeze-dried and, if desired, combined with other pharmaceutically acceptable excipients to prepare formulations for administration. These compositions may be presented in any form appropriate for the administration route envisaged. The parenteral and the intravenous route are the preferential routes for administration.





Compounds of the general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium



carboxymethylcellulose, methyl cellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia: dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example hepta-decaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl-*p*-hydroxy benzoate, one or more colouring agents, one or more flavouring agents or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example peanut oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin.

The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or peanut oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.



Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or a suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compound(s) of the general Formula I may be administered, together or separately, in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compound(s) of general Formula I may be administered, together or separately, parenterally in sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

The dosage to be administered is not subject to defined limits, but it will usually be an effective amount. It will usually be the equivalent, on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active free drug to achieve its desired pharmacological and physiological effects. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.



The active compound is effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.01 to about 30 mg/kg of body weight. A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 mg to about 500 mg, more preferably about 25 mg to about 300 mg of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.





***Formulation 1***

Hard gelatin capsules are prepared using the following ingredients:

	<b>Quantity (mg/capsule)</b>
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

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***Formulation 2***

A tablet is prepared using the ingredients below:

	<b>Quantity (mg/tablet)</b>
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665

The components are blended and compressed to form tablets each weighing 665 mg.

***Formulation 3***

An aerosol solution is prepared containing the following components:



	Weight %
Active Ingredient	0.25
Ethanol	29.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	100

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30 °C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

---

#### *Formulation 4*

Tablets each containing 60 mg of active ingredient are made as follows:

	Quantity (mg/tablet)
Active Ingredient	60
Starch	45
Microcrystalline cellulose	35
Polyvinylpyrrolidone	4
Sodium carboxymethyl starch	4.5
Magnesium stearate	0.5
Talc	1.0
Total	150

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders that are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed



through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

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#### ***Formulation 5***

Capsules each containing 80 mg medicament are made as follows:

	<b>Quantity (mg/capsule)</b>
Active Ingredient	80
Starch	59
Microcrystalline cellulose	59
Magnesium stearate	2
Total	200

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 sieve, and filled into hard gelatin capsules in 200 mg quantities.

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#### ***Formulation 6***

Suppositories each containing 225 mg of active ingredient may be made as follows:

	<b>Quantity (mg/suppository)</b>
Active Ingredient	225
Saturated fatty acid glycerides	2000
Total	2225

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.



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*Formulation 7*

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

Active Ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mL
Benzoic acid solution	0.10 mL
Flavour	q.v.
Color	q.v.
Purified water to total	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

---

*Formulation 8*

An intravenous formulation may be prepared as follows:

	Quantity
Active Ingredient	100 mg
Mannitol	100 mg
5 N Sodium hydroxide	200 mL
Purified water to total	5 mL

---

*Formulation 9*

A topical formulation may be prepared as follows:





	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White soft paraffin to	100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

---

#### *Formulation 10*

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

	Quantity (mg/tablet)
Active Ingredient	10.0
Glycerol	210.5
Water	143.0
Sodium Citrate	4.5
Polyvinyl Alcohol	26.5
Polyvinylpyrrolidone	15.5
Total	410.0

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90 °C. When the polymers have gone into solution, the solution is cooled to about 50°-55 °C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size.



Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts.

The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, for example, U.S. Pat. No. 5,023,252, issued Jun. 11, 1991) herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Pat. No. 5,011,472, issued Apr. 30, 1991, which is herein incorporated by reference.

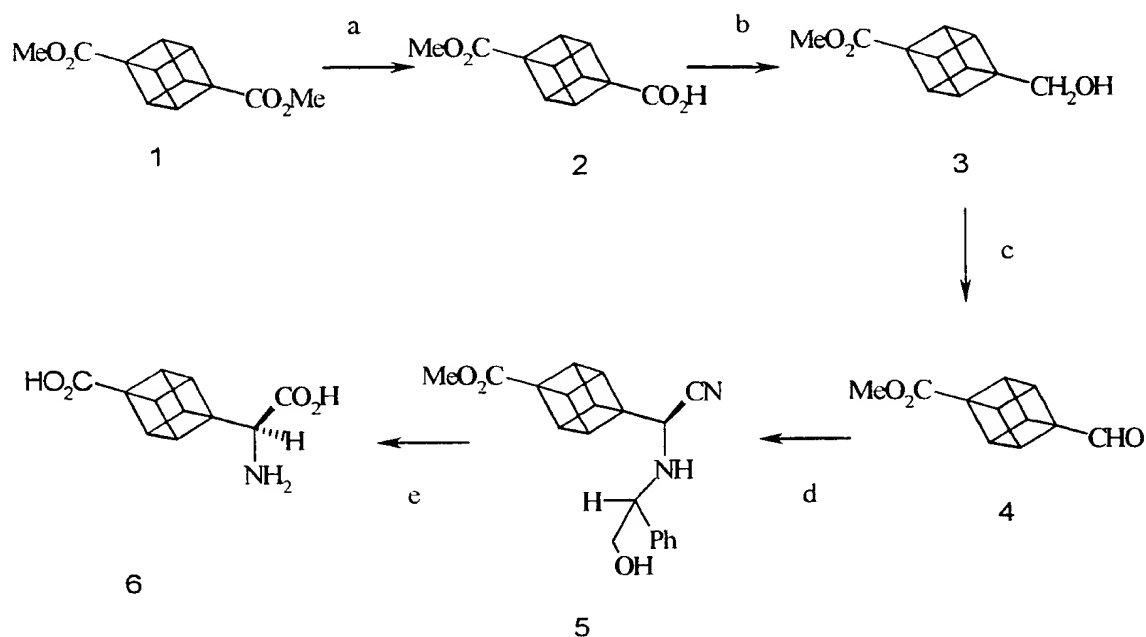
Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions that can transiently open the blood-brain barrier.

## EXAMPLES

The following Examples illustrate the invention. The following abbreviations are used in the Examples: EtOAc, ethyl acetate; THF, tetrahydrofuran; EtOH, ethanol; TLC, thin layer chromatography; GC, gas chromatography; HPLC, high pressure liquid chromatography; m-CPBA, m-chloroperbenzoic acid; Et<sub>2</sub>O, diethyl ether; DMSO, dimethyl sulfoxide; DBU, 1,8-diazabicyclo-[5.4.0]undec-7-ene; MTBE, methyl *t*-butyl ether; FDMS, field desorption mass spectrometry and r.t., room temperature.



## Example 1: Synthesis of Cubanylglycinates IGT 1.0 series

*Preparation 1: 4-methoxycarbonylcubane carboxylic acid*

A solution of cubane dimethyl ester (6.0g, 27.24 mmol) in 182 mL of dry THF is stirred under  $N_2$  at room temperature. A solution of methanolic NaOH (26.7 mmol, 10.7 mL 2.5 M) is added dropwise from a pressure equalized addition funnel and the resulting solution stirred at room temperature for 16 h. The mixture is evaporated under reduced pressure at r.t., the residue is taken up in 66 mL of water and extracted with 3 x 25 mL of chloroform. The aqueous layer is acidified to pH 3 with concentrated HCl and extracted with 3 x 30 mL of chloroform. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give (2) 182-183 °C:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.72 (s, 3H), 4.27 (m, 6H).

Yield 5.1 g (91%).

*Preparation 2: 4-methoxycarbonyl-1-(hydroxymethyl) cubane*

The mono acid (2) (0.48 g) is dissolved in dry THF (5 mL) and cooled to -70 °C. A solution of  $BH_3$  in THF is added slowly with stirring. The reaction mixture is stirred at -78 °C for 4 hrs and



allowed to come to room temperature. Water (3 mL) is added and stirred for 30 min, potassium carbonate (0.85 g) is added and the solution extracted with Et<sub>2</sub>O. The organic phase is dried over magnesium sulfate and evaporated to give the alcohol (3) 0.46 g (100%) m.p. 83-85 °C. <sup>1</sup>H NMR(200 MHz, solvent) δ: 1.58 (s, 1H), 3.62 (s, 3H), 3.72 (s, 2H), 3.81 (m, 3H), 4.1 (m, 3H).

*Preparation 3: 4-methoxycarbonyl-1-(formyl) cubane*

DMSO (0.7 mL, 9.68 mmol) is added to oxalyl chloride (0.42 mL, 4.84 mmol) in 12 mL of CH<sub>2</sub>Cl<sub>2</sub> at -78 °C. The alcohol (3) (0.46 g, 2.42 mmol) in 3 mL CH<sub>2</sub>Cl<sub>2</sub> is added and stirred at -78 °C for 1.5 h. Triethylamine (2.0 mL, 14.4 mmol) is added and the mixture is allowed to come to 0°C. Saturated ammonium chloride solution is added and the phases separated, the aqueous layer is extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers are dried (MgSO<sub>4</sub>), then evaporated to give crude product which is purified by flash chromatography (1:1 hexanes:diethyl ether) to give 0.35 g (76%) of pure product (4). <sup>1</sup>H NMR (200 MHz, solvent) δ: 3.7 (s, 3H), 4.2 (m, 3H), 4.32 (m, 3H), 9.72 (s, 1H).

*Preparation 4: 4-methoxycarbonyl-1-[2'-hydroxy-1'-phenylethyl] methylnitrilecubane*

(*R*)-phenylglycinol (257 mg, 1.87 mmol) is added to a solution of the aldehyde (4) (0.35 g, 1.84 mmol) in 14 mL of methanol. The solution is cooled to 0 °C and TMSCN (0.49 mL, 3.68 mmol) is added and the mixture stirred at 0 °C overnight. Evaporation of the solvent leaves a residue which is purified by chromatography (diethyl ether:hexanes, 3:1) to give 0.48 g (77%) of pure product (5). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.23 (s, 1H), 2.6 (br, 1H), 3.5-3.75 (m, 2H), 3.7 (s, 3H), 3.9 (m, 3H), 4.11 (dd, 1H), 4.2 (m, 3H), 7.3 (s, 5H).

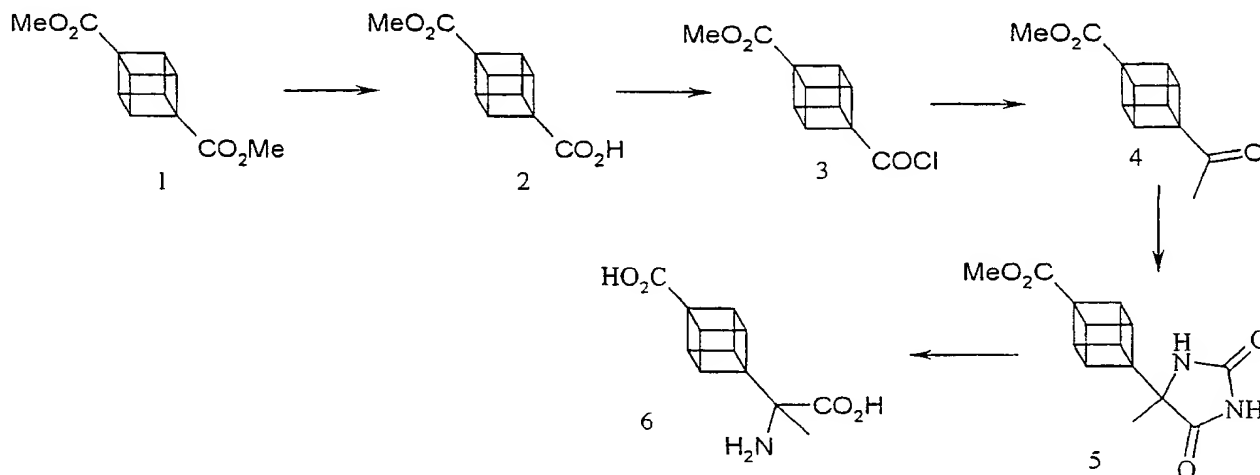
*Preparation 5: 4-carbonyl-1-cubanylglycine*

Lead acetate (0.69 g, 1.57 mmol) is added to a stirred solution of nitrile (5) (0.48 g, 1.42 mmol) in dry methanol/dichloromethane 1:1 (12 mL). After 10 min 10 mL of water is added and the suspension filtered through celite. The organic layer is dried and evaporated to give the crude imine. The crude imine is refluxed with 6N HCl (30 mL) for 6 hr. The solution is evaporated to dryness and placed on anion exchange resin, eluting with 1N acetic acid to yield the product (6). mp. 241 °C (dec.) <sup>1</sup>H NMR (D<sub>2</sub>O) δ 3.96 (s, 1H), 4.01 (m, 3H), 4.14 (m, 3H).





## Example 2

*Preparation 1: 4-methoxycarbonylcubane carboxylic acid*

A solution of cubane dimethyl ester (6.0g, 27.24 mmol) in 182 mL of dry THF is stirred under  $N_2$  at r.t. a solution of methanolic NaOH (26.7 mmol, 10.7 mL 2.5 M) is added dropwise from a pressure equalized addition funnel and the resulting solution stirred at r.t. for 16 h. The mixture is evaporated under reduced pressure at r.t., the residue is taken up in 66 mL of water and extracted with 3 x 25 mL of chloroform. The aqueous layer is acidified to pH 3 with concentrated HCl and extracted with 3 x 30 mL of chloroform. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give (2) 182-183 °C:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.72 (s, 3H), 4.27 (m, 6H).

Yield 5.1 g (91%).

*Preparation 2: 4-methoxycarbonylcubane-1-carbonyl chloride*

The monomethyl ester (2) (1.37 g, 6.65 mmol) is dissolved in 15 mL of thionyl chloride and gently refluxed overnight. The thionyl chloride is evaporated off and the resultant residue containing (3) was used immediately without further purification.



*Preparation 3: 4-methoxycarbonylcubane-1-methyl ketone*

A suspension of copper iodide (1.49 g, 7.83 mmol) in 30 mL of dry THF is stirred at 0°C. Methyl lithium (15.75 mmol, 11.2 mL of 1.4 M) was added and stirred at 0°C for 30 min, then cooled to -78°C. A solution of 1.6 g, 7.12 mmol of (3) in 10 mL dry THF is added and the resultant mixture stirred for 1 h. at -78°C. The mixture was quenched with saturated ammonium chloride solution (15 mL) and extracted with 3 x 30 mL of diethyl ether. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give crude (4). The product was purified by silica chromatography (hexanes:ethyl acetate, 2:1) to give 1.0 g of product (yield 69%). m.p. 87-89°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.17 (s, 3H), 3.7 (s, 3H), 4.21 (m, 6H).

*Preparation 4: 4-methoxycarbonylcubane-1-methyl-1-(5,5'-hydantoin)*

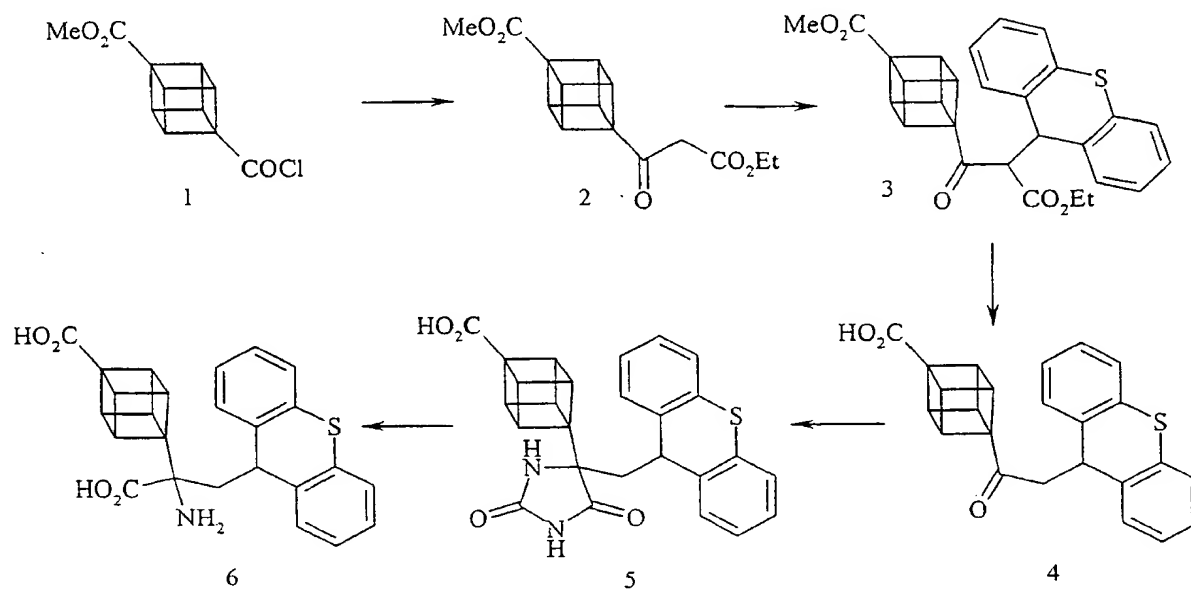
A solution of the methyl ketone (4) (1.0 g, 4.9 mmol) in 40 mL of ethanol and 5.8 mL of 1 N NaOH, is stirred at 70°C for 4 h. The resulting solution is evaporated to dryness under reduced pressure and redissolved in 1:1 ethanol: water (20 mL). To this solution is added potassium cyanide (0.35 g, 5.4 mmol) and ammonium carbonate (0.96 g, 9.8 mmol) and the mixture heated in a sealed tube at 85°C for 24 h. The reaction is cooled, acidified with 6 N HCl and reduced in volume until a precipitate forms. The precipitate is filtered and the filtrate evaporated to dryness and extracted with ethyl acetate. The solvent is evaporated and the product combined with the residue from above to give (5) as a white solid. Yield 0.95 g (75%) m.p. 244-248°C. NMR <sup>1</sup>H (DMSO) δ 1.18 (s, 3H) 3.9 (m, 3H), 4.0 (m, 3H), 8.1 (s, 1H), 10.6 (s, 1H).

*Preparation 5: 4-carboxycubane-1-methylglycine*

The hydantoin (5) (0.95 g, 3.65 mmol) is dissolved in 30 mL of 2 N NaOH and heated to 170°C in a sealed tube for 20 h. The reaction is cooled and filtered to remove precipitate and the filter cake washed with 3 x 10 mL of water. The combined aqueous washings are evaporated to give crude (6) which is applied to Spectrum 1X4 anion exchange resin, eluted with 0.5 N acetic acid. Isolation by evaporation and crystallization gives (6) as colorless crystals. m.p. >250°C (decomp.). NMR. <sup>1</sup>H (D<sub>2</sub>O) δ 1.38 (s, 3H), 3.95 (s, 6H).



## Example 3

*Preparation 1: 4-methoxycarbonylcubane-1-acetyl ethylcarboxylate.*

n-butyl lithium (34.83 mmol, 23.5 mL of 1.5 M) is added dropwise to a stirred solution of ethyl hydrogen malonate (2.32 g, 17.41 mmol) in 80 mL of dry THF under  $\text{N}_2$  at  $-78^\circ\text{C}$ . The mixture was warmed to  $-30^\circ\text{C}$  over 0.5 h and then re-cooled to  $-78^\circ\text{C}$ . The acid chloride of cubane monomethyl ester from example (2) above (2.35 g, 10.46 mmol) in 7 mL of THF is added dropwise to the stirred solution. The reaction is warmed slowly to r.t and stirred for a further 1 h. The solution is poured into 50 mL of 1 N HCl and extracted with 3 x 50 mL of diethyl ether. The combined organic extracts are further extracted with 20 mL of saturated sodium hydrogen carbonate and brine, dried over magnesium sulphate, filtered and evaporated to give crude (2). The product is purified by column chromatography on silica with hexanes: ethyl acetate 2:1 to yield 2.5 g (86%) of (2).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.2 (t, 3H) 3.4 (s, 2H), 3.65 (s, 3H), 4.2 (m, 8H).



*Preparation 2: 4-methoxycarbonylcubane-1-(thioxanthyl)-acetyl ethylcarboxylate.*

cubane- $\beta$ -ketoester (2) (1.15g, 4.16 mmol) and thioxanthene-9-ol (0.88g, 4.1 mmol) are dissolved in 18 mL of a 1:1 mixture of ethanol:acetic acid and stirred at r.t. for 3 days. The resulting crystalline solid was filtered off to yield 1.52 g (77%) of pure (3) m.p. 147-149°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.00 (t, 3H), 3.24 (s, 3H), 3.75 (m, 3H), 3.9 (q, 2H), 4.0 (m, 3H), 4.6 (d, 1H), 5.0 (d, 1H), 7.3 (m, 8H).

*Preparation 3: 4-carboxycubane-1-methylthioxanthylketone*

The thioxanthylcubane adduct (3) (1.69 g, 3.57 mmol) is dissolved in ethanol 33 mL and 8.7 mL of 1 N NaOH and heated at 70°C for 4 h. The resulting solution is evaporated and redissolved in 25 mL of water, acidified with 6 N HCl and extracted with 3 x 50 mL of diethyl ether. The combined organic layers are dried over magnesium sulphate, filtered and concentrated to give a crude product containing (4). Chromatography on silica using ethyl acetate gives 1.26 g (88%) of (4)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.8 (d, 2H), 3.8 (m, 3H), 4.0 (m, 3H), 4.7 (t, 1H), 7.3 (m, 8H), 9.5 (br, 1H).

*Preparation 4: 4-carboxycubane-1-thioxanthyl-1-(5,5'-hydantoin)*

The thioxanthyl cubane ketone (4) (1.24 g, 3.22 mmol) is dissolved in 1:1 ethanol:water (20 mL). Potassium cyanide (0.522 g, 8.0 mmol) and ammonium carbonate (1.39 g, 14.4 mmol) are added and the solution heated in a sealed tube at 85°C for 65 h. The reaction is cooled and acidified with 2 N HCl and extracted with 3 x 40 mL of ethyl acetate. The organic layers are combined, dried over magnesium sulphate, filtered and evaporated to give (5) 1.3 g (88%) as a crude product. This material was hydrolyzed in the next step without purification.

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.7 (m, 1H), 2.7 (m, 1H), 3.8 (m, 3H), 4.0 (m, 3H), 4.3 (m, 1H), 7.4 (m, 8H).

*Preparation 5: 4-carboxycubane-1- thioxanthyl Iglycine*



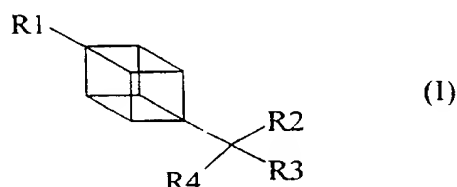


The hydantoin adduct (5) (300 mg, 0.65 mmol) is taken up in 1 N NaOH (10 mL) and heated at 170 °C for 20 h in a sealed tube. The mixture is cooled and the pH adjusted with 6 N HCl to between 7 and 8. The precipitate formed is filtered and washed with water. The combined filtrate and washings are combined and evaporated to dryness. The resulting residue is purified by column chromatography and finally by reverse phase chromatography to yield (6) as colorless crystals. 70 mg. <sup>1</sup>H NMR (CD<sub>3</sub>OD + D<sub>2</sub>O) δ 2.3 (m, 2H), 3.9 (s, 6H), 4.4 (m, 1H), 7.4 (m, 8H).



We claim:

1. A compound of the formula:



wherein:

**R1** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfinio, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, and -CH<sub>2</sub>-isoxazol;

**R2** can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea,

**R3** can be H, aliphatic, aromatic or heterocyclic;

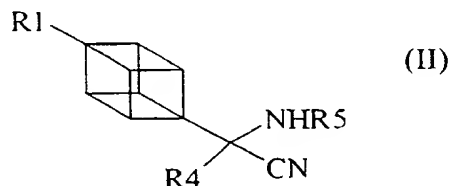
**R4** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol; and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, wherein **R1** is COOH



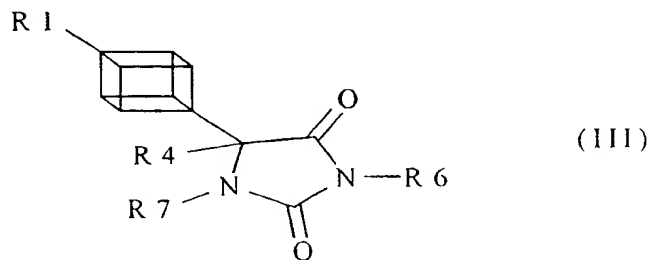
3. A compound as claimed in claim 1, wherein **R2** is COOH
4. A compound as claimed in claim 1, wherein **R3** can be -H, or -Me; or xanthyl or thioxanthyl and **R4** is NH<sub>2</sub>
5. A process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolyzing a compound of formula:



in which **R1** is defined as above, **R5** represents a hydrogen atom or an acyl group and **R4** has the meaning defined above. Preferred values for **R5** are hydrogen and (2-6C) alkanoyl groups, such as acetyl;

(b) hydrolyzing a compound of formula:

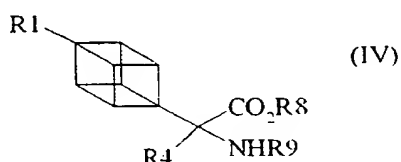


wherein **R6** and **R7** each independently represent a hydrogen atom, a (2-6C) alkanoyl



group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof, or

(c) deprotecting a compound of formula:



in which **R8** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R9** represents a hydrogen atom or a nitrogen protecting group;

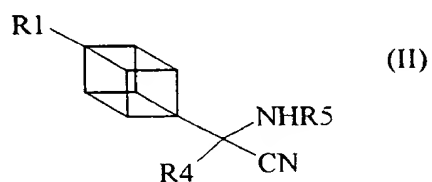
whereafter, if necessary and/or desired:

- (i) resolving the compound of Formula I;
  - (ii) converting the compound of Formula I into a non-toxic metabolically-labile ester or amide thereof; and/or;
  - (iii) converting the compound of Formula I or a non-toxic metabolically-labile ester or amide thereof into a pharmaceutically acceptable salt thereof.
6. A pharmaceutical formulation, which comprises a compound as claimed in claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.
7. A method of modulating one or more metabotropic glutamate receptor functions in a warm blooded mammal requiring such treatment, which comprises administering an effective amount of a compound as claimed in claim 1.



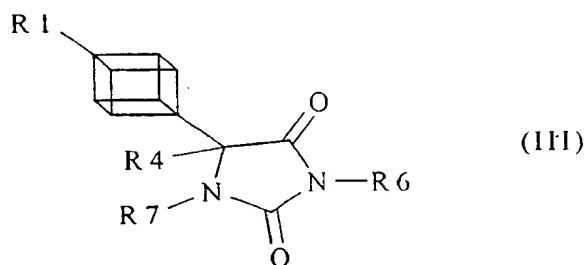


8. A compound of formula:



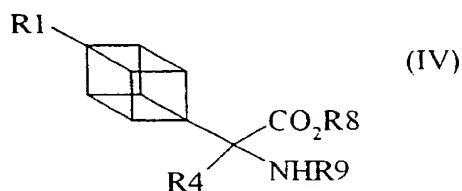
in which **R1**, **R4** and **R5** have the meanings as defined above.

9. A compound of formula:



wherein **R6** and **R7** have meanings as defined above.

10. A compound of formula:

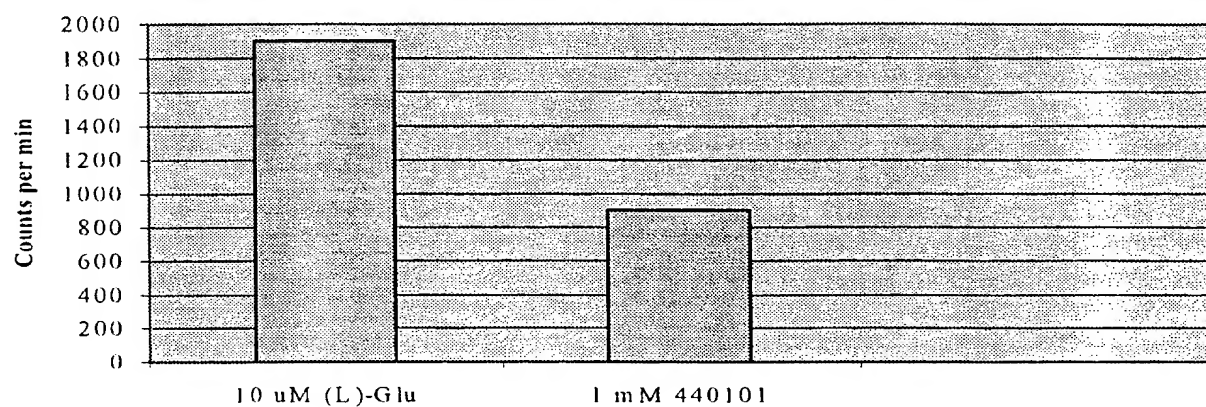


in which **R8** and **R9** have meanings as defined above.



Figure 1

The Actions of a Compound of the Invention as an Antagonist of PI Hydrolysis  
evoked through the mGluR1 receptor by 10  $\mu$ M (L)-Glu





# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/CA 99/00311

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C229/28 C07C229/46 A61K31/195 C07D233/78 C07F9/38  
C07D335/12 C07F5/02 C07C309/27

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C A61K C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	<p>PELLICCIARI R ET AL: "Synthesis and preliminary evaluation of (S)-2-(4'-carboxycubyl)glycine, a new selective mGluR1 antagonist"</p> <p>BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 12, 16 June 1998 (1998-06-16), page 1569-1574 XP004137086</p> <p>ISSN: 0960-894X</p> <p>the whole document</p> <p style="text-align: center;">--- -/--</p>	1-8, 10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 August 1999

Date of mailing of the international search report

30/08/1999

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Rufet, J



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00311

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>KOZIKOWSKI A P ET AL: "alpha-substituted quisqualic acid analogs: New metabotropic glutamate receptor group II selective antagonists"</p> <p>BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 5, 3 March 1998 (1998-03-03), page 447-452 XP004136882</p> <p>ISSN: 0960-894X</p> <p>the whole document</p> <p>---</p>	1,6,7
A	<p>MARINOZZI M ET AL: "Asymmetric synthesis of enantiomerically pure (2S,1'S,2'S,3'R)-phenylcarboxycyclopropylglycine (PCCG-4): a potent and selective ligand at group II metabotropic glutamate receptors"</p> <p>BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 18, 17 September 1996 (1996-09-17), page 2243-2246 XP004135693</p> <p>ISSN: 0960-894X</p> <p>the whole document</p> <p>---</p>	1,6,7
A	<p>TOMS N J ET AL: "THE EFFECTS OF (RS)-ALPHA-CYCLOPROPYL-4-PHOSPHONOPHENYLGLYCINE ((RS)-CPPG), A POTENT AND SELECTIVE METABOTROPIC GLUTAMATE RECEPTOR ANTAGONIST"</p> <p>BRITISH JOURNAL OF PHARMACOLOGY, vol. 119, no. 5, 1 January 1996 (1996-01-01), pages 851-854, XP000618728</p> <p>ISSN: 0007-1188</p> <p>the whole document</p> <p>---</p>	1,6,7
A	<p>US 5 238 958 A (NOVAK PERRY M ET AL)</p> <p>24 August 1993 (1993-08-24)</p> <p>abstract; claims 1-22</p> <p>---</p>	1,6,7
A	<p>WO 97 19049 A (CIBA GEIGY AG ;SANDOZ AG (DE); NOVARTIS ERFINDUNGEN VERWALTUN (AT))</p> <p>29 May 1997 (1997-05-29)</p> <p>claims 1-11</p> <p>---</p>	1,6,7
A	<p>WO 97 21715 A (UNIV BRISTOL ;TOCRIS COOKSON LIMITED (GB); WATKINS JEFFREY CLIFTON)</p> <p>19 June 1997 (1997-06-19)</p> <p>page 1 - page 3; claims 1-9</p> <p>-----</p>	1,6,7





# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/00311

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: **1 PARTLY**  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



## INTERNATIONAL SEARCH REPORT

International Application No. PCT/CA 99 00311

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 partly

Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to formula (I) of claim 1, wherein R4 is carboxyl and R1, R2 and R3 have the definitions given in claim 1 (no restriction for those substituents).

The subject-matter of claims 2 to 10 have been searched completely.

It is stressed that the subject-matter of the depending claims 3 and 4 is unclear. The definitions of R2 and R4 of claims 3 and 4 respectively are unclear, since those definitions are different from the definitions of R2 and R4 of claim 1.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00311

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5238958	A	24-08-1993	NONE	
WO 9719049	A	29-05-1997	IT MI952383 A AU 7627496 A	19-05-1997 11-06-1997
WO 9721715	A	19-06-1997	NONE	



1  
2  
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4  
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# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

# PCT

To:

MBM & CO.  
P.O. Box 809, Station B  
Ottawa, Ontario K1P 5P9  
CANADA

## NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence  
and Administrative Instructions, Section 601(a))

Date of mailing  
(day/month/year)

26. 11. 99

Applicant's or agent's file reference

379-110PCT

### IMPORTANT NOTIFICATION

International application No.

PCT/CA 99/ 00311

International filing date (day/month/year)

19/04/1999

Priority date (day/month/year)

17/04/1998

Applicant

CURRY, Kenneth et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

17/11/1999

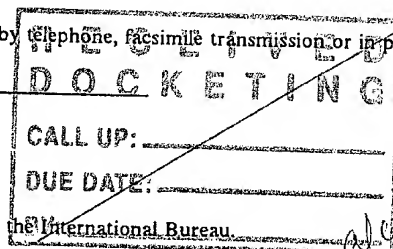
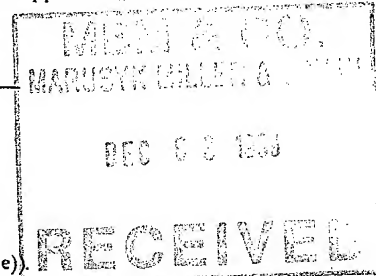
2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).  
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).  
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand, (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.



Name and mailing address of the IPEA/

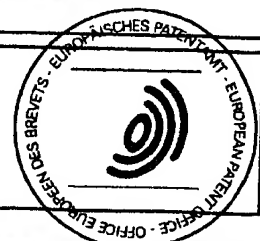


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Fax: (+49-89) 2399-4465

Authorized officer

VON KEMPIS B G M

Tel. (+49-89) 2399-8577







## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C. 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 13 December 1999 (13.12.99)	<b>Applicant's or agent's file reference</b> 379-110PCT
<b>International application No.</b> PCT/CA99/00311	<b>Priority date (day/month/year)</b> 17 April 1998 (17.04.98)
<b>International filing date (day/month/year)</b> 19 April 1999 (19.04.99)	<b>Applicant</b> CURRY, Kenneth et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
17 November 1999 (17.11.99)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  <p style="text-align: center;">Juan Cruz</p> Telephone No.: (41-22) 338.83.38
---	--

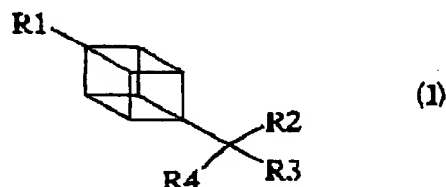


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We claim:

1. A compound of the formula:



wherein:

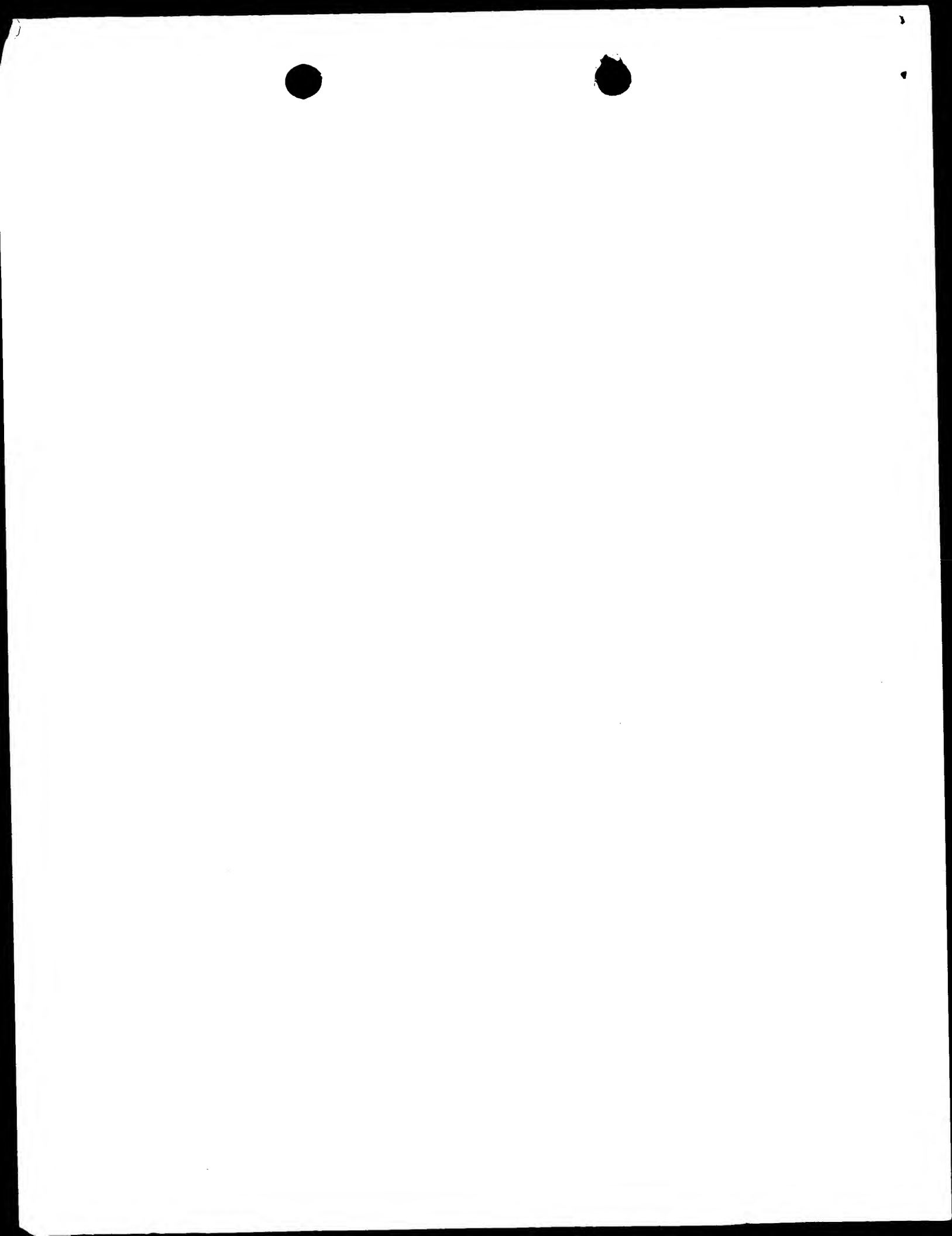
R1 can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfino, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, and -CH<sub>2</sub>-isoxazol;

R2 can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea,

R3 can be H, aliphatic, aromatic or heterocyclic;

R4 can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfino, borono, tetrazol, isoxazol; and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, wherein R1 is COOH.
3. A compound as claimed in claim 1, wherein R2 is NH<sub>2</sub>.

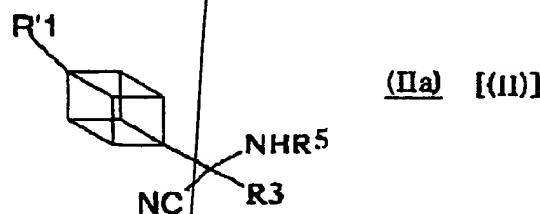


20-07-2000

CA 009900311

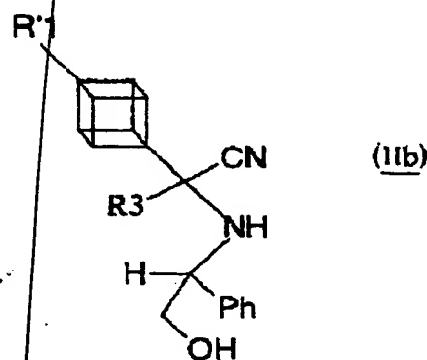
4. A compound as claimed in claim 1, wherein R<sub>3</sub> can be -H, or -Me; or xanthyl or thioxanthyl or -CH<sub>2</sub>-xanthyl, or -CH<sub>2</sub>-thioxanthyl and R<sub>4</sub> is -COOH.
5. A process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolyzing a compound of formula:

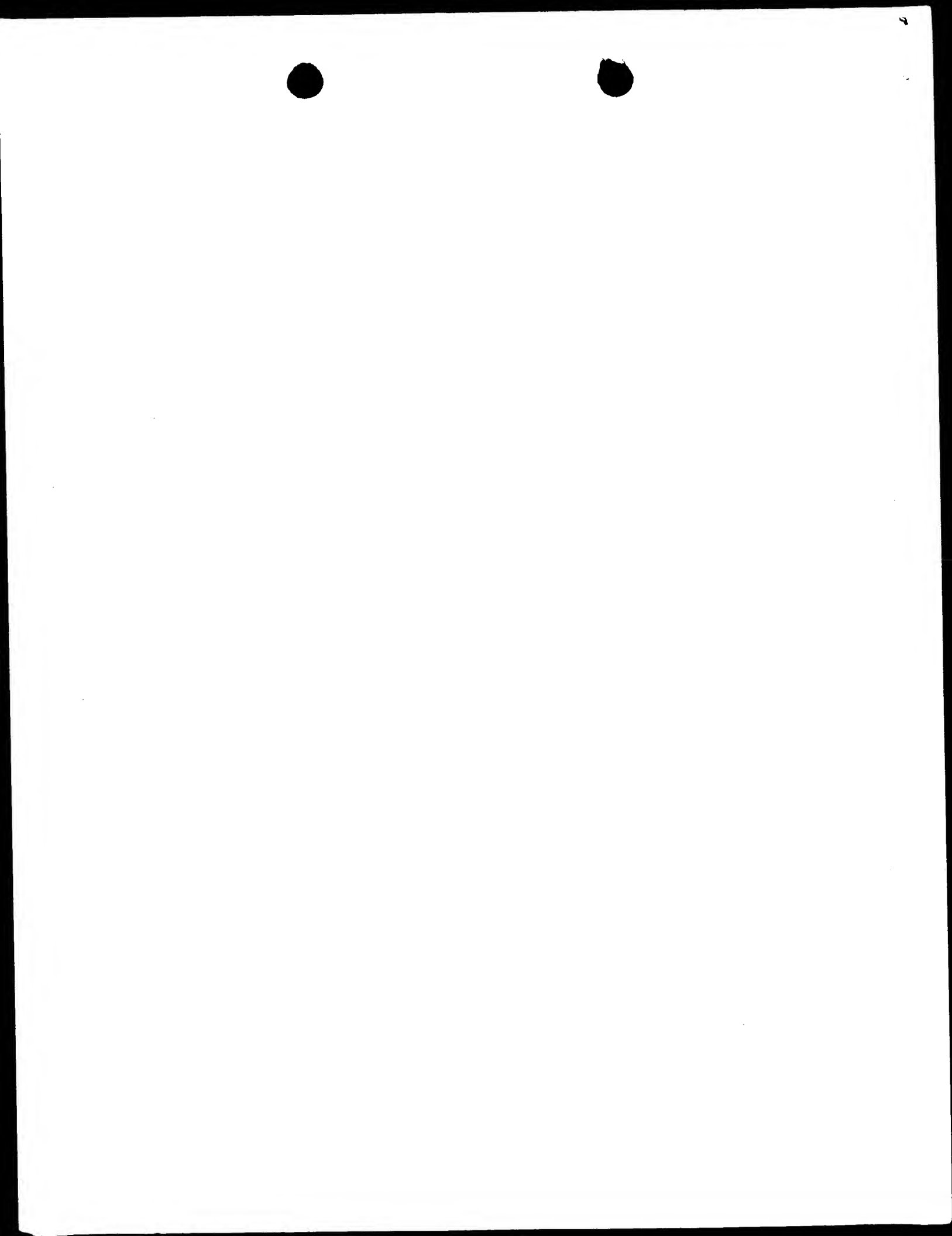


wherein: R'1 is an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfinio, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, -CH<sub>2</sub>-isoxazol and higher analogues thereof, or a protected form thereof, R<sub>3</sub> can be H, aliphatic, aromatic or heterocyclic and [in which R<sub>1</sub> is defined as above,] R<sub>5</sub> represents a hydrogen atom or an acyl group [and R<sub>4</sub> has the meaning defined above,], and wherein [P] preferred values for R<sub>5</sub> are hydrogen and (2-6C) alkanoyl groups, such as acetyl; or

(b) deprotecting and hydrolyzing a compound of formula (II b)



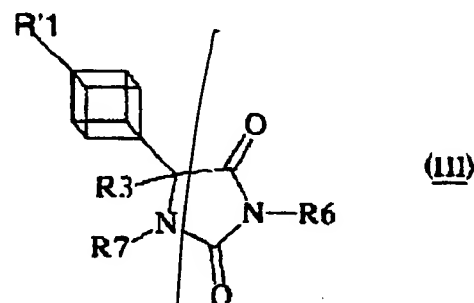
wherein: R'1 and R<sub>3</sub> are as defined above; or



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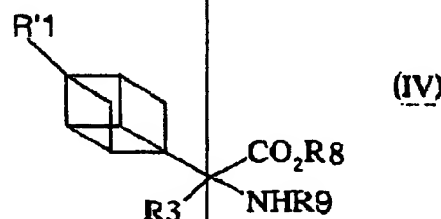
CA 009900311

- (c) [b] hydrolyzing a compound of formula:



wherein: **R6** and **R7** each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof, **R'1** and **R3** are as defined above; or

- (d) [c] deprotecting a compound of formula:

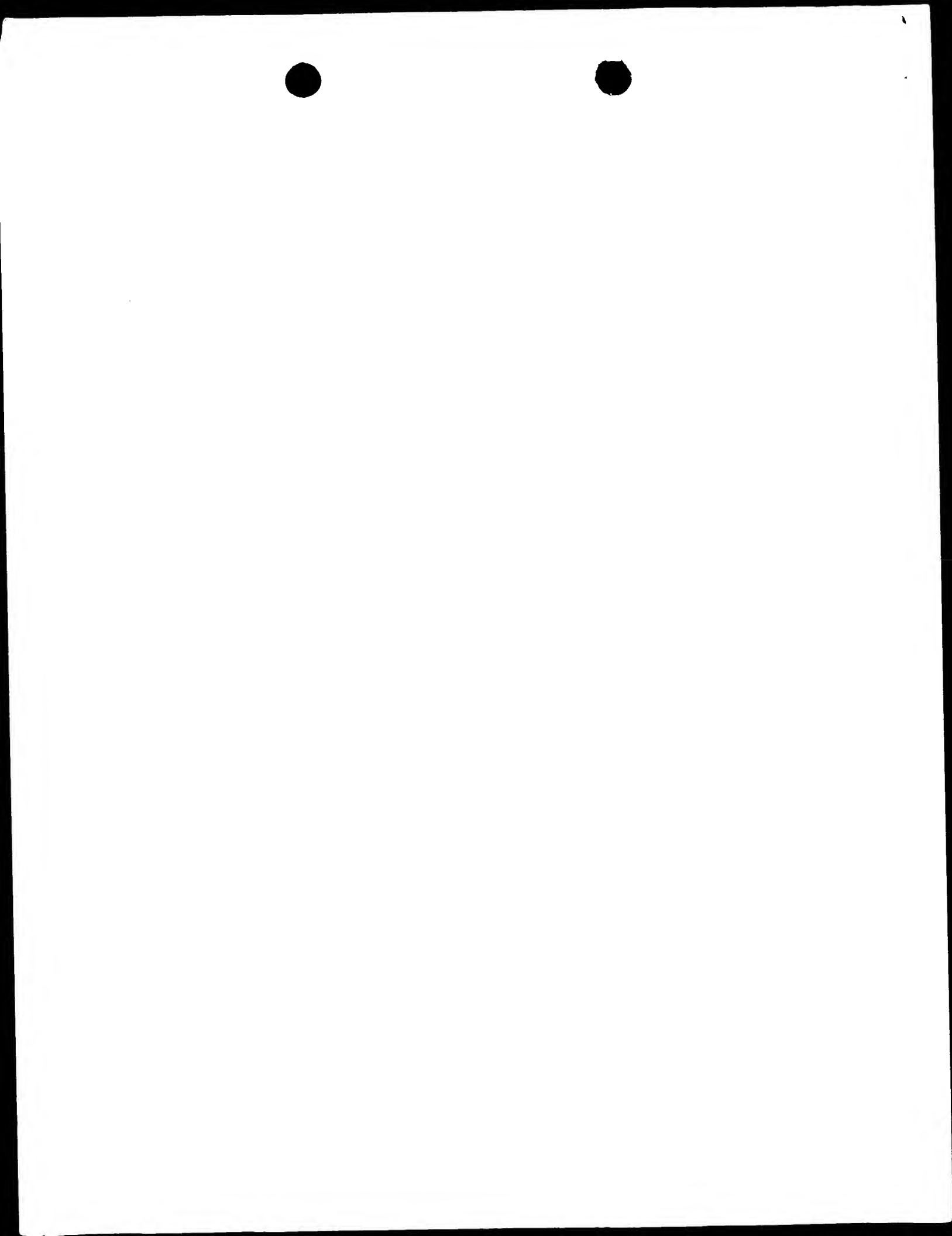


wherein: [in which] **R8** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R9** represents a hydrogen atom or a nitrogen protecting group, **R'1** and **R3** are as defined above;

whereafter, if necessary and/or desired:

- (i) resolving the compound of Formula I;
- (ii) converting the compound of Formula I into a non-toxic metabolically-labile ester or amide thereof; and/or;
- (iii) converting the compound of Formula I or a non-toxic metabolically-labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

6. A pharmaceutical formulation, which comprises a compound as claimed in claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.



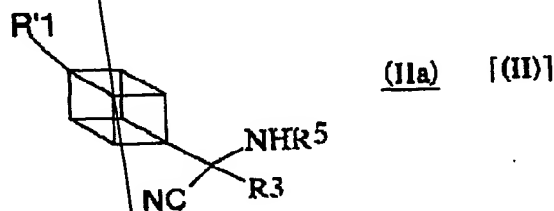


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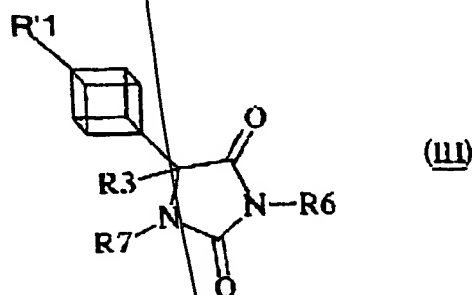
7. A use of the compound according to claim 1 to modulate [A method of modulating] one or more metabotropic glutamate receptor functions in a warm blooded mammal [requiring such treatment], wherein said use [which] comprises administering an effective amount of a compound of formula (I) as claimed in claim 1.

8. A compound of formula:

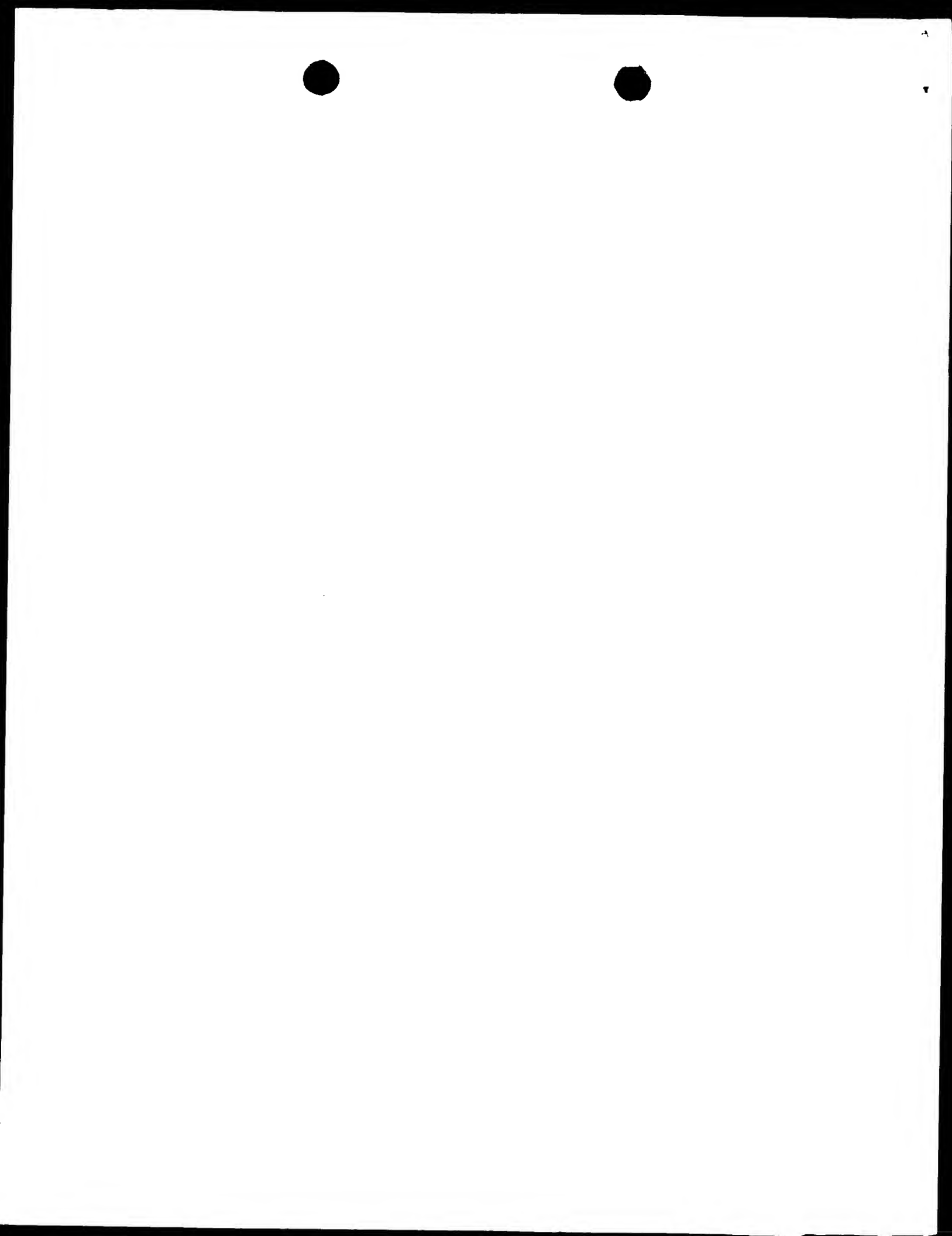


wherein: R'1, R3 and R5 have the meanings as defined in claim 5 [in which R1, R4 and R5 have the meanings as defined above].

9. A compound of formula:



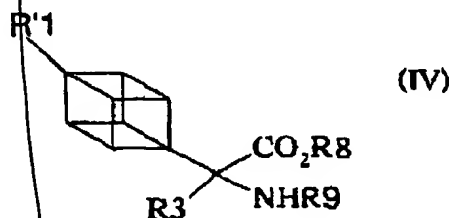
wherein: R'1, R3, R6 and R7 have meanings as defined in claim 5 [wherein R6 and R7 have meanings as defined above].



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10. A compound of formula:



wherein: R'1, R3, R8 and R9 have meanings as defined in claim 5 [in which R8 and R9 have meanings as defined above].

11. A compound according to claim 1, wherein R1 is -COOH, R2 is -NH<sub>2</sub>, R3 is H and R4 is COOH.
12. A compound according to claim 1, wherein R1 is -COOH, R2 is -NH<sub>2</sub>, R3 is CH<sub>3</sub> and R4 is COOH.
13. A compound according to claim 1, wherein R1 is -COOH, R2 is -NH<sub>2</sub>, R3 is -CH<sub>2</sub>-thioxanthyl and R4 is COOH.
14. A use of the compound according to claim 1 for the treatment of a neurological disease or disorder selected from the group comprising: cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia, stroke, cardiac arrest, spinal cord trauma, head trauma, perinatal hypoxia, and hypoglycemic neuronal damage, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, anxiety and related disorders (e.g. panic attack), emesis, brain edema, chronic pain, sleep disorders, Tourette's syndrome, attention deficit disorder, and tardive dyskinesia, wherein said use comprises administering an effective amount of a compound of formula (I).

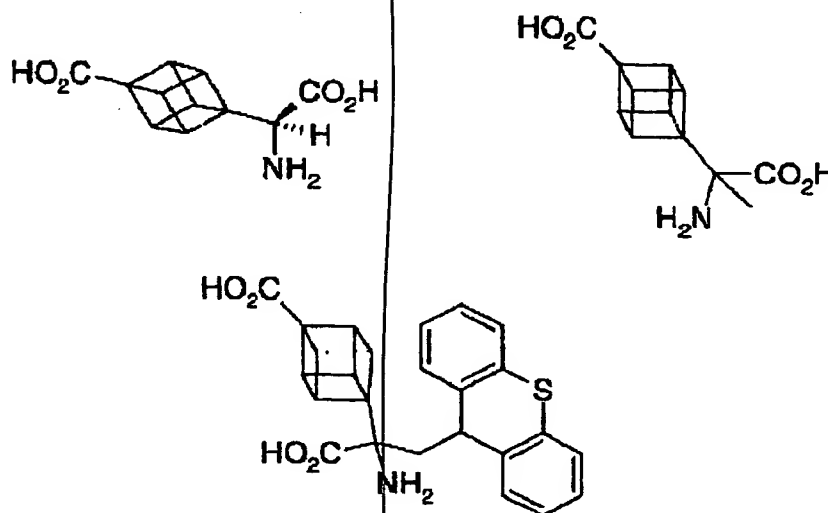


20-07-2000

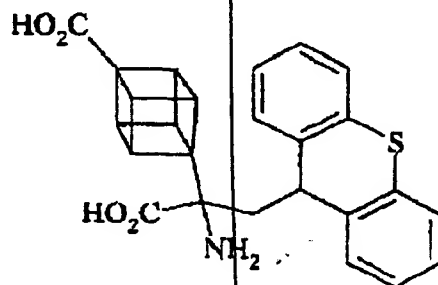
CA 009900311

15. A use of the compound according to claim 1 for the treatment of a psychiatric disease or disorder selected from the group comprising: schizophrenia, anxiety and related disorders (c.g. panic attack), depression, bipolar disorders, psychosis, and obsessive compulsive disorders, wherein said use comprises administering an effective amount of a compound of formula (I).

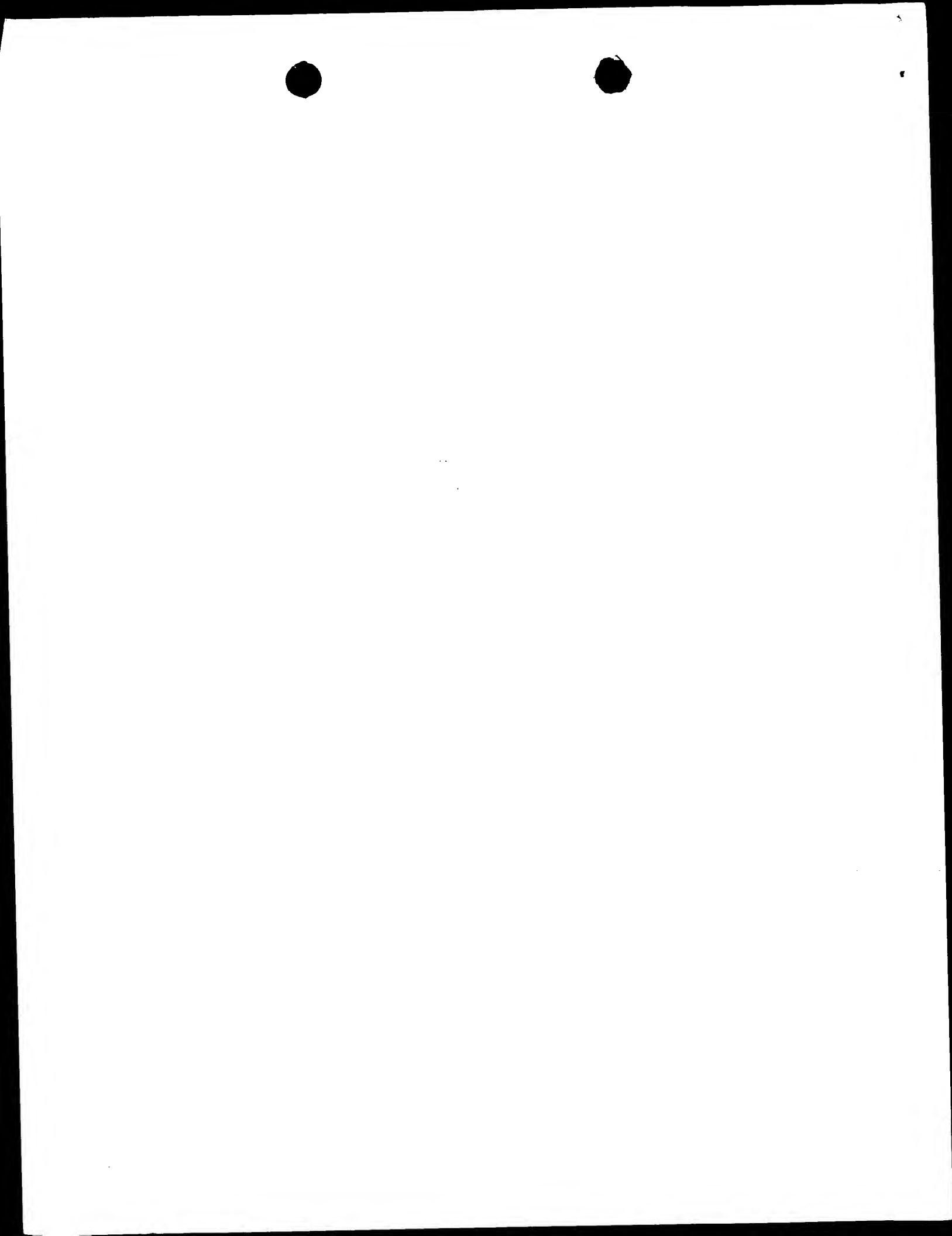
16. The use according to any one of claims 7, 14 or 15 wherein said compound is selected from the group of compounds comprising :



17. A use of the compound:



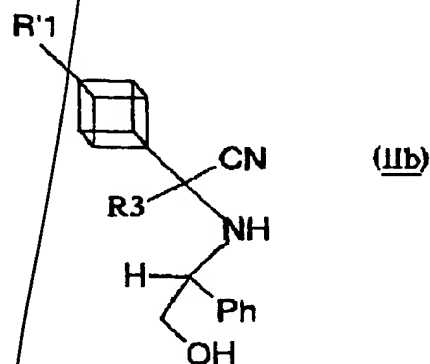
for the treatment of cerebral ischemia, stroke and cardiac arrest, wherein said use comprises administering an effective amount of the said compound.



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CA 009900311

18. A compound of formula:

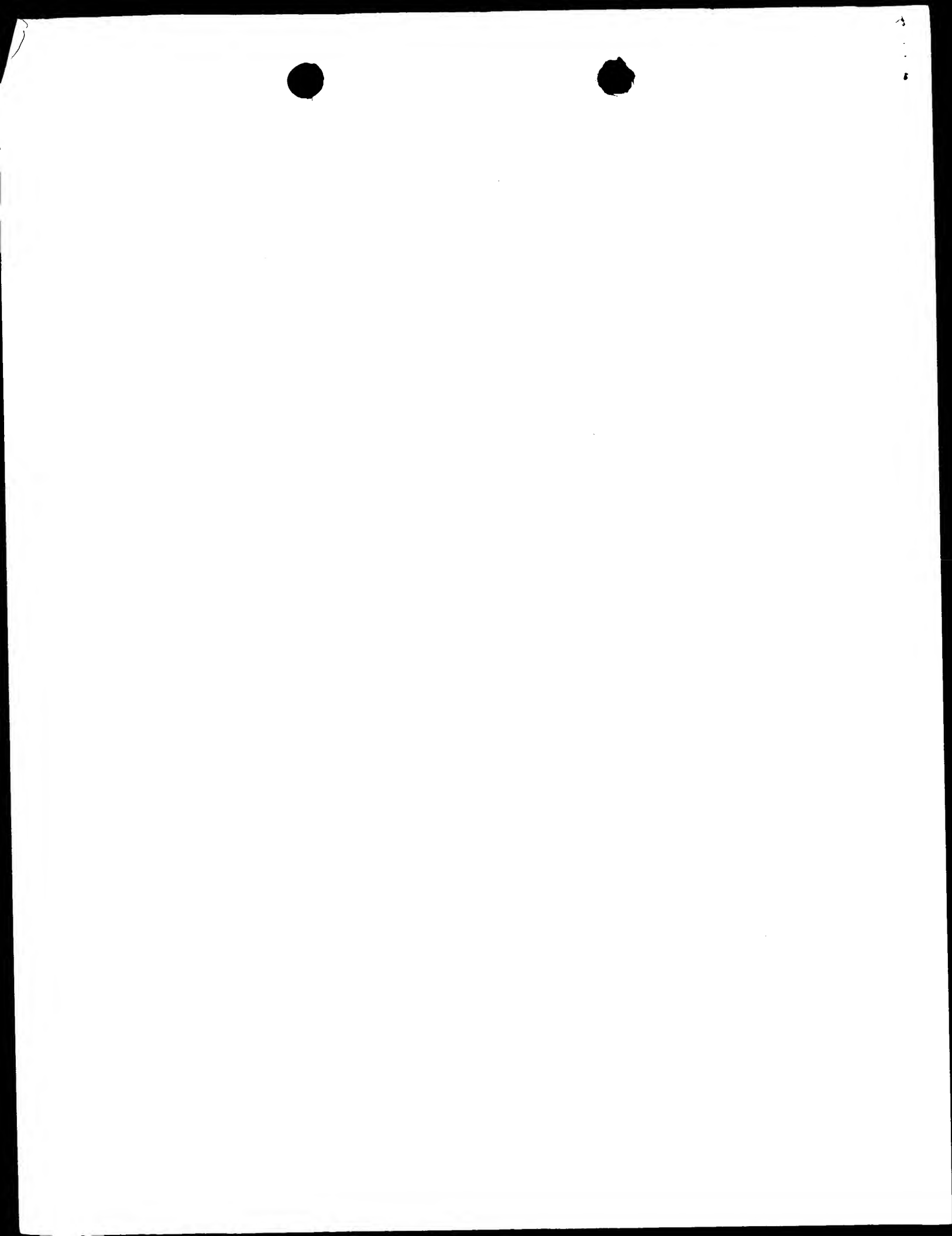


wherein: R'1 and R3 have the meaning as defined in claim 5.

19. A compound according to claim 18, wherein: R'1 is -COOMe, R3 is H.

20. A compound according to claim 9, wherein: R'1 is -COOH, R3 is CH<sub>3</sub>, R6 = R7 is H.

21. A compound according to claim 9, wherein: R'1 is -COOH, R3 is -CH<sub>2</sub>-thioxanthyl, R6 = R7 is H.





E. J.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>379-110PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/CA 99/ 00311</b>	International filing date (day/month/year) <b>19/04/1999</b>	(Earliest) Priority Date (day/month/year) <b>17/04/1998</b>
Applicant <b>CURRY, Kenneth et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

**4. With regard to the title,**

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

**CUBANE DERIVATIVES AS METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS AND PROCESS FOR THEIR PREPARATION**

**5. With regard to the abstract,**

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/00311

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: **1 PARTLY**  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 partly

Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to formula (I) of claim 1, wherein R4 is carboxyl and R1, R2 and R3 have the definitions given in claim 1 (no restriction for those substituents).

The subject-matter of claims 2 to 10 have been searched completely.

It is stressed that the subject-matter of the depending claims 3 and 4 is unclear. The definitions of R2 and R4 of claims 3 and 4 respectively are unclear, since those definitions are different from the definitions of R2 and R4 of claim 1.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



## INTERNATIONAL SEARCH REPORT

International Application No

CT/CA 99/00311

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C229/28 C07C229/46 A61K31/195 C07D233/78 C07F9/38  
C07D335/12 C07F5/02 C07C309/27

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C A61K C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	PELLICCIARI R ET AL: "Synthesis and preliminary evaluation of (S)-2-(4'-carboxycubyl)glycine, a new selective mGluR1 antagonist" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 12, 16 June 1998 (1998-06-16), page 1569-1574 XP004137086 ISSN: 0960-894X the whole document --- -/--	1-8, 10

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

20 August 1999

Date of mailing of the international search report

30/08/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Rufet, J





## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00311

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>KOZIKOWSKI A P ET AL: "alpha-substituted quisqualic acid analogs: New metabotropic glutamate receptor group II selective antagonists"</p> <p>BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 5, 3 March 1998 (1998-03-03), page 447-452 XP004136882</p> <p>ISSN: 0960-894X</p> <p>the whole document</p>	1,6,7
A	<p>MARINOZZI M ET AL: "Asymmetric synthesis of enantiomerically pure (2S,1'S,2'S,3'R)-phenylcarboxycyclopropylglycine (PCCG-4): a potent and selective ligand at group II metabotropic glutamate receptors"</p> <p>BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 18, 17 September 1996 (1996-09-17), page 2243-2246 XP004135693</p> <p>ISSN: 0960-894X</p> <p>the whole document</p>	1,6,7
A	<p>TOMS N J ET AL: "THE EFFECTS OF (RS)-ALPHA-CYCLOPROPYL-4-PHOSPHONOPHENYLGLYCINE ((RS)-CPPG), A POTENT AND SELECTIVE METABOTROPIC GLUTAMATE RECEPTOR ANTAGONIST"</p> <p>BRITISH JOURNAL OF PHARMACOLOGY, vol. 119, no. 5, 1 January 1996 (1996-01-01), pages 851-854, XP000618728</p> <p>ISSN: 0007-1188</p> <p>the whole document</p>	1,6,7
A	<p>US 5 238 958 A (NOVAK PERRY M ET AL)</p> <p>24 August 1993 (1993-08-24)</p> <p>abstract; claims 1-22</p>	1,6,7
A	<p>WO 97 19049 A (CIBA GEIGY AG ; SANDOZ AG (DE); NOVARTIS ERFINDUNGEN VERWALTUN (AT))</p> <p>29 May 1997 (1997-05-29)</p> <p>claims 1-11</p>	1,6,7
A	<p>WO 97 21715 A (UNIV BRISTOL ; TOCRIS COOKSON LIMITED (GB); WATKINS JEFFREY CLIFTON) 19 June 1997 (1997-06-19)</p> <p>page 1 - page 3; claims 1-9</p>	1,6,7



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00311

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5238958	A	24-08-1993	NONE		
WO 9719049	A	29-05-1997	IT	MI952383 A	19-05-1997
			AU	7627496 A	11-06-1997
WO 9721715	A	19-06-1997	NONE		



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**PATENT COOPERATION TREATY**

**PCT**

REC'D 24 OCT 2000

WIPO

PCT

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 379-110PCT		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/CA99/00311	International filing date (day/month/year) 19/04/1999	Priority date (day/month/year) 17/04/1998	
International Patent Classification (IPC) or national classification and IPC C07C229/28			
Applicant CURRY, Kenneth et al.			

**RECEIVED**  
MAR 20 2001  
TECH CENTER 1600/2000


- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 5 sheets, including this cover sheet.
  - ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 45 sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

**CORRECTED  
VERSION**

Date of submission of the demand  17/11/1999	Date of completion of this report  18.10.2000
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Butkowskyj-Walkiw, T  Telephone No. +49 89 2399 8594





**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/CA99/00311

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

37,38	as originally filed			
1-7,9,10,16-30, 32-36	as received on	28/07/1999	with letter of	09/07/1999
8,11,11a,12-15, 31	as received on	20/07/2000	with letter of	20/07/2000

**Claims, No.:**

1-21	as received on	20/07/2000	with letter of	20/07/2000
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**Drawings, sheets:**

1	as received on	28/07/1999	with letter of	09/07/1999
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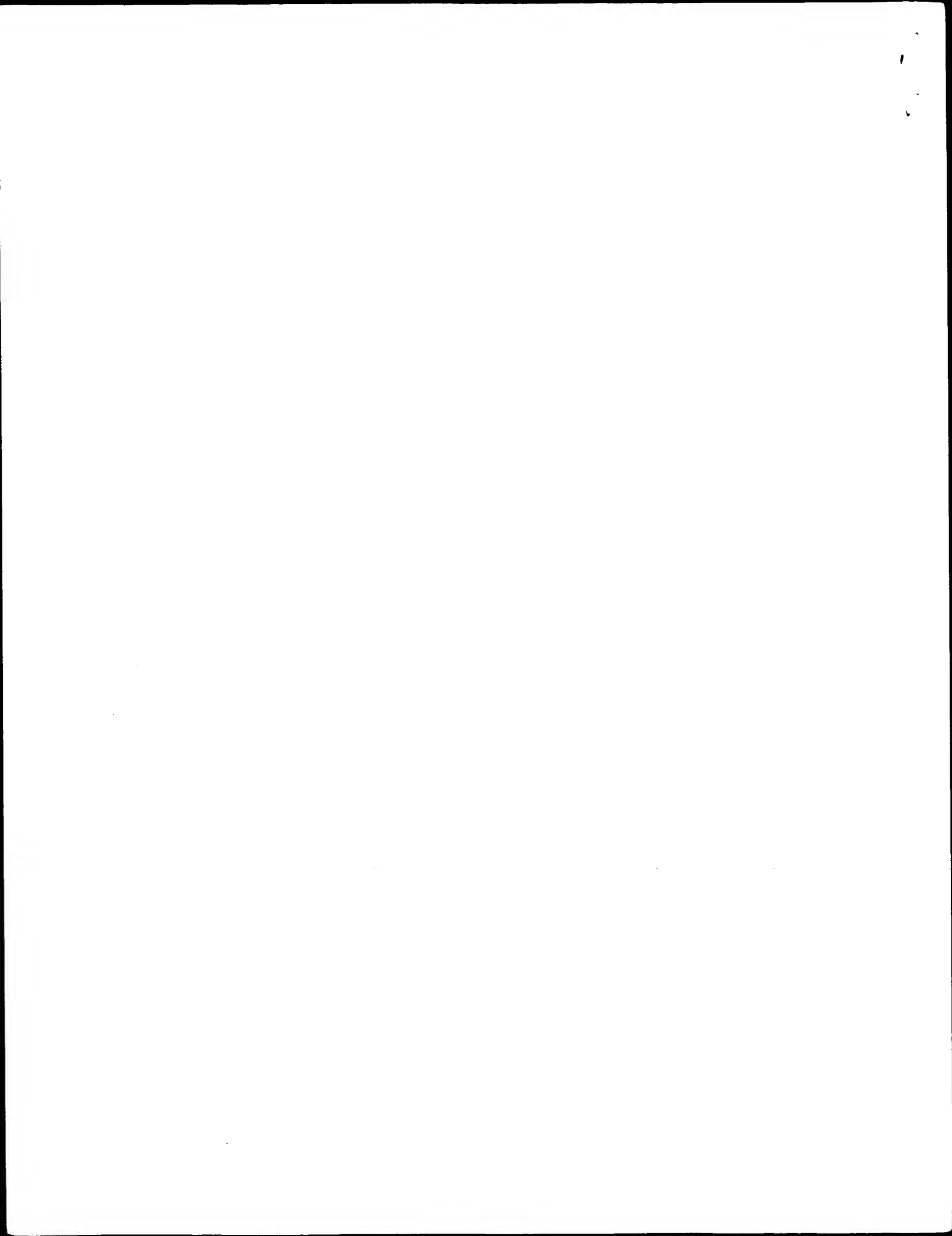
2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

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# **INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

International application No. PCT/CA99/00311

## **V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

### **1. Statement**

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6,8-13,18-21
	No:	Claims	

### **2. Citations and explanations**

**see separate sheet**

## **VI. Certain documents cited**

### **1. Certain published documents (Rule 70.10)**

and / or

### **2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

## **VII. Certain defects in the international application**

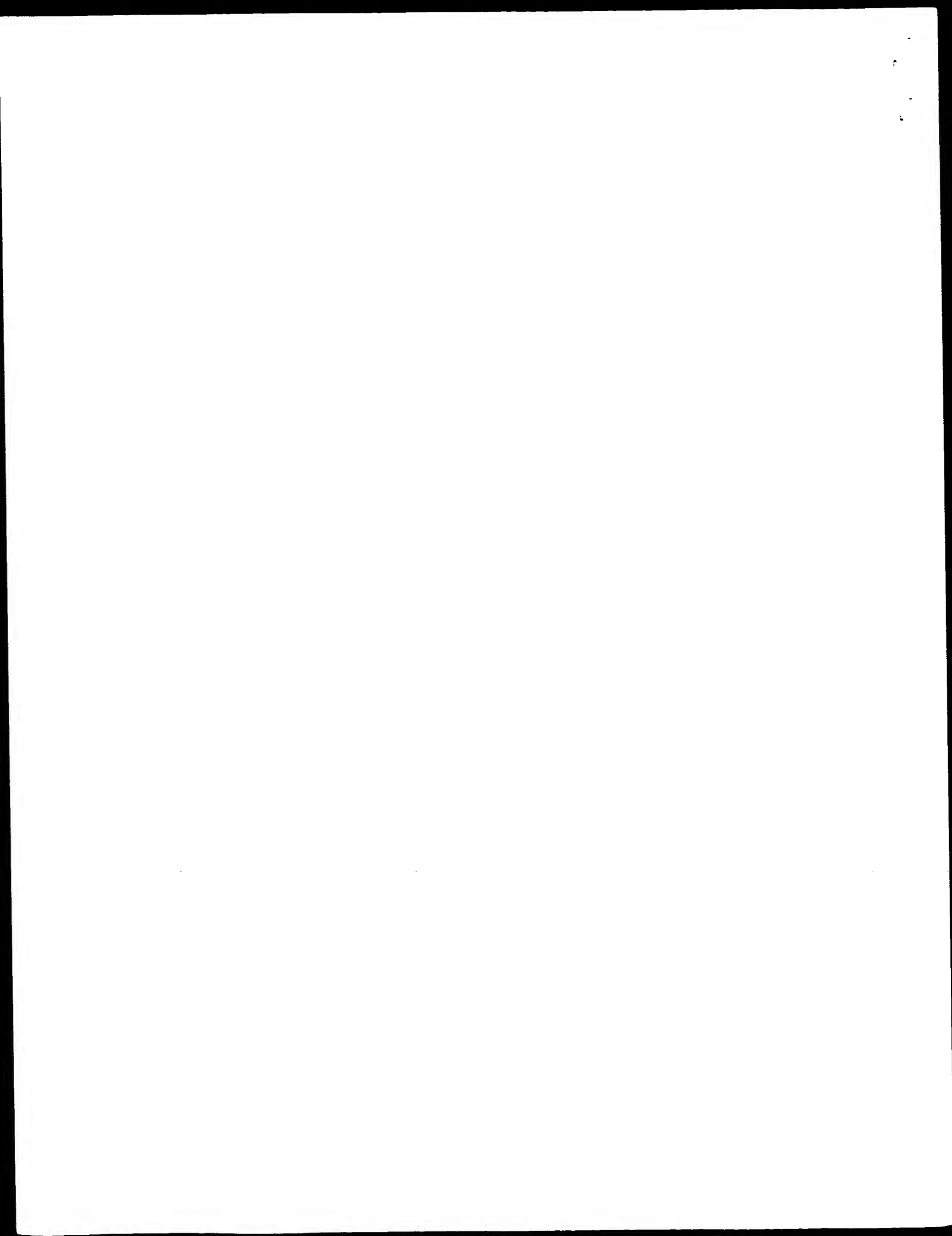
The following defects in the form or contents of the international application have been noted:

**see separate sheet**

## **VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**



**V.**

In the light of the documents cited in the search report the present claims 1-21 can be considered as being novel (Art. 33(2) PCT).

Further, the present claims 1-21 can be considered as being inventive (Art. 33(3) PCT) as the object of the present application, namely to provide compounds that demonstrate activity at the various metabotropic glutamate receptors (mGluRs), and the presently claimed solution have not been suggested by any of the cited prior art documents. D1 (PELLICCIARI et al, Asymmetric Synthesis of Enantiomerically pure (2S,1'S,2'S,3'R)-Phenylcarboxycyclopropylglycine, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 18, pages 2243-2246, 1996) which can be considered as closest prior art document refers to cyclopropyl analogs and in the light of this teaching it was not obvious for a skilled person to arrive at the present subject-matter.

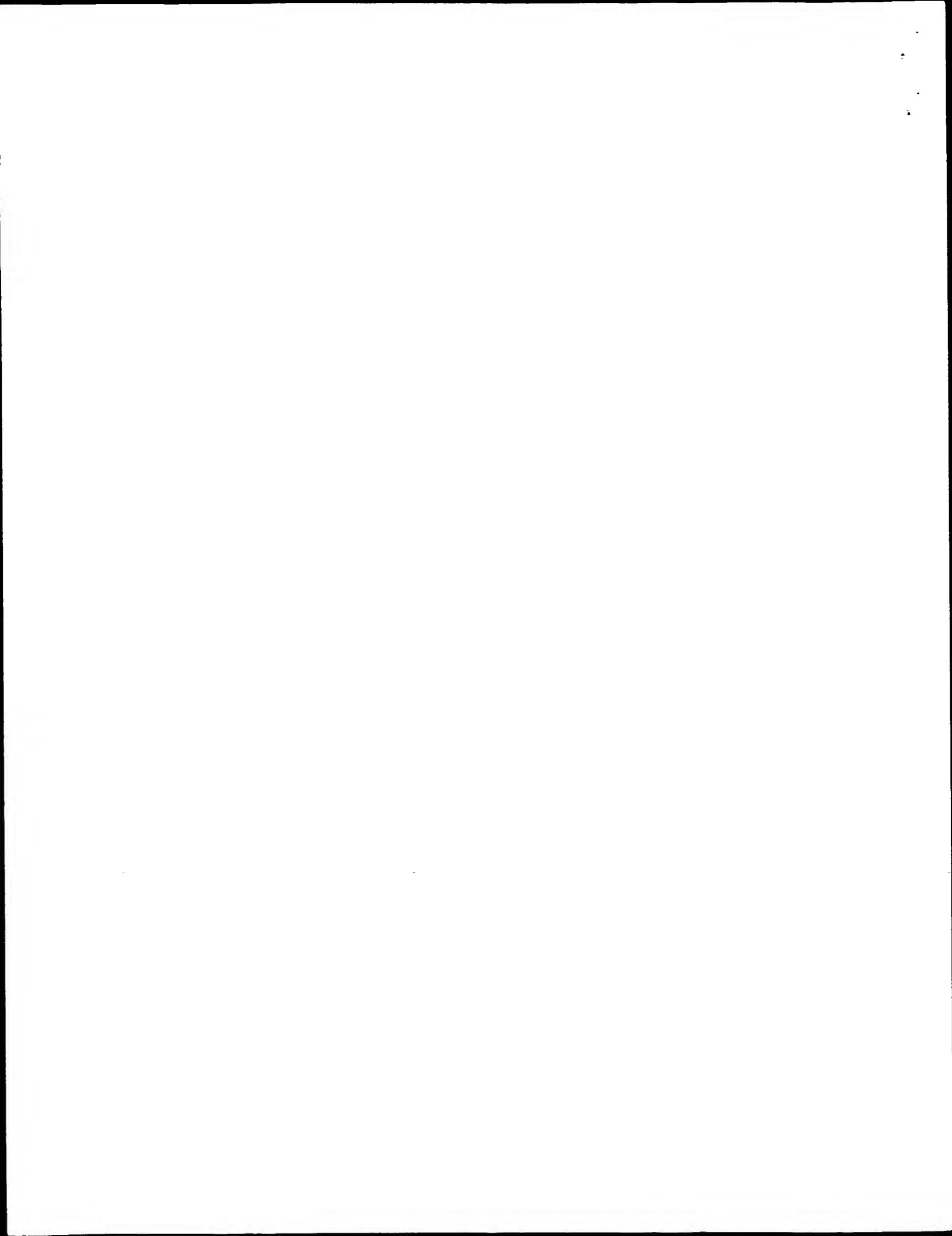
For the assessment of the present claims 7,14-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**VI.**

The present application claims priority rights from 17/4/98. The priority document pertaining to the present application was not available at the time of establishing this report. Hence it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D2 (PELLICCIARI et al: "Synthesis and preliminary evaluation of (S)-2-(4'-carboxycubyl)glycine, a new selective mGluR1 antagonist" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 12, 16/6/98, pages 1569-1574), cited in the search report would become very relevant in the assessment of the patentability of the present application.

**VII.**

The amendments in on pages 8,11,12,14 and claims 4,5,13,16,17 and 21 filed with the letter dated 20/7/00 introduce subject-matter which extends beyond the content of the



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/CA99/00311

application as filed, contrary to Article 34(2)(b) PCT.

**VIII.**

The term "aliphatic" (claim 1) without any indication of the number of carbon atoms is too broad in scope and therefore unclear (Art. 6 PCT).

Further, expressions as "the like" and "about" with reference to ranges are unclear.



## CUBANE ANALOGS WITH ACTIVITY AT THE METABOTROPIC GLUTAMATE RECEPTORS

### FIELD OF THE INVENTION

This invention pertains to therapeutically active cubane derivatives, a method for preparing the same, pharmaceutical compositions comprising the compounds and a method of treating diseases of the Central Nervous System (CNS) therewith.

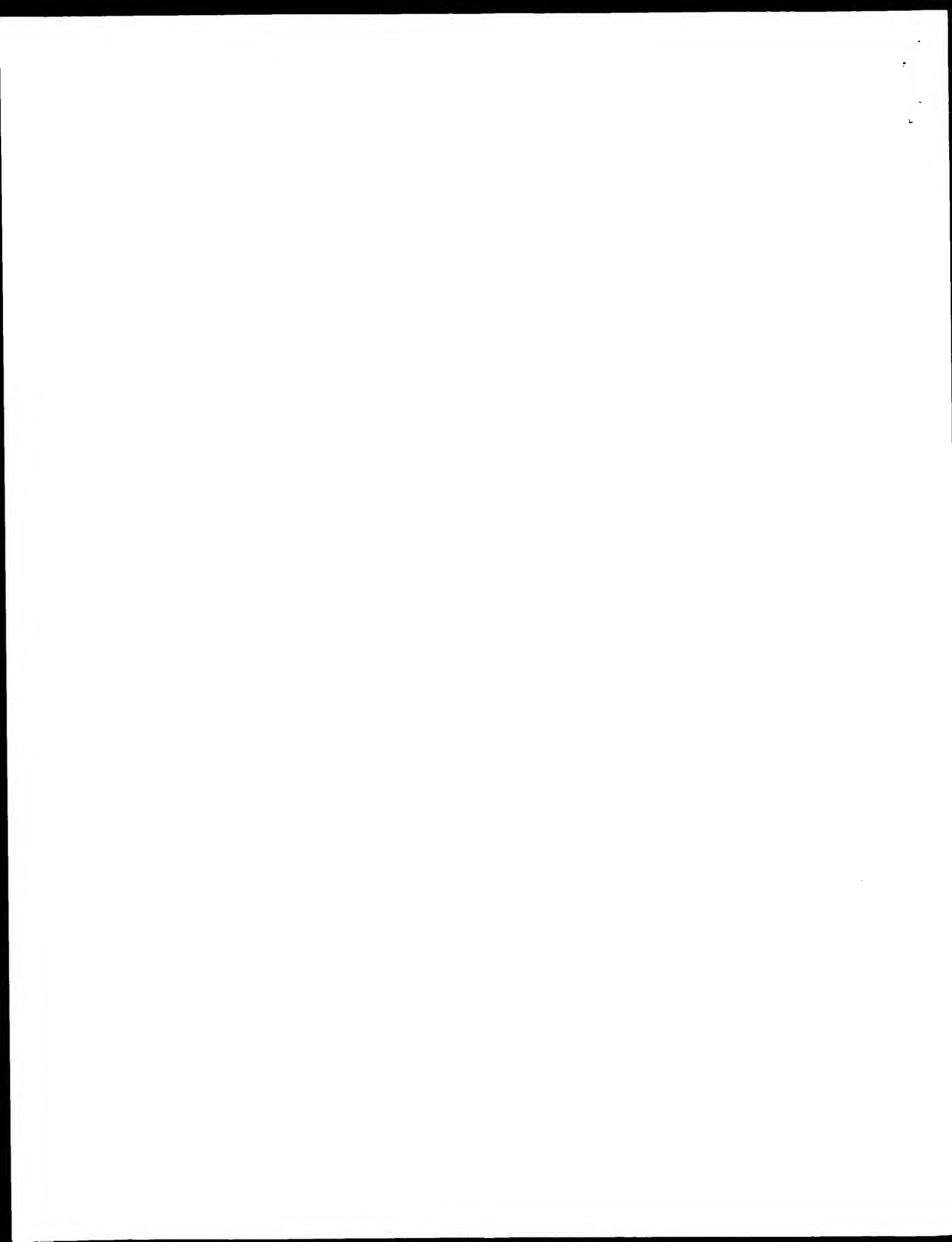
### BACKGROUND OF THE INVENTION

The acidic amino acid L-Glutamate is recognized as the major excitatory neurotransmitter in the CNS. The receptors that respond to L-Glutamate are called excitatory amino acid receptors. The excitatory amino acid receptors are thus of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiratory and cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types and both are activated by L-Glutamic acid and its analogs. Receptors activated by L-Glutamic acid that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic." This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists N-Methyl-D-aspartate (NMDA),  $\alpha$ -Amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and Kainic acid (KA).

The second general type of receptor is the G-protein or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D, increases or decreases in cAMP formation, and changes in ion channel function (Schoepp and Conn, *Trends in Pharmacological Science*, 14:13, 1993). Both types of receptors appear not only to mediate normal synaptic transmission along excitatory pathways but also to participate in the modification of synaptic connections during development and throughout life.

So far eight different clones of the G-protein-coupled metabotropic glutamate receptors (mGluRs) have been identified (Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426). These receptors function to modulate the presynaptic release of L-Glutamate, and the postsynaptic



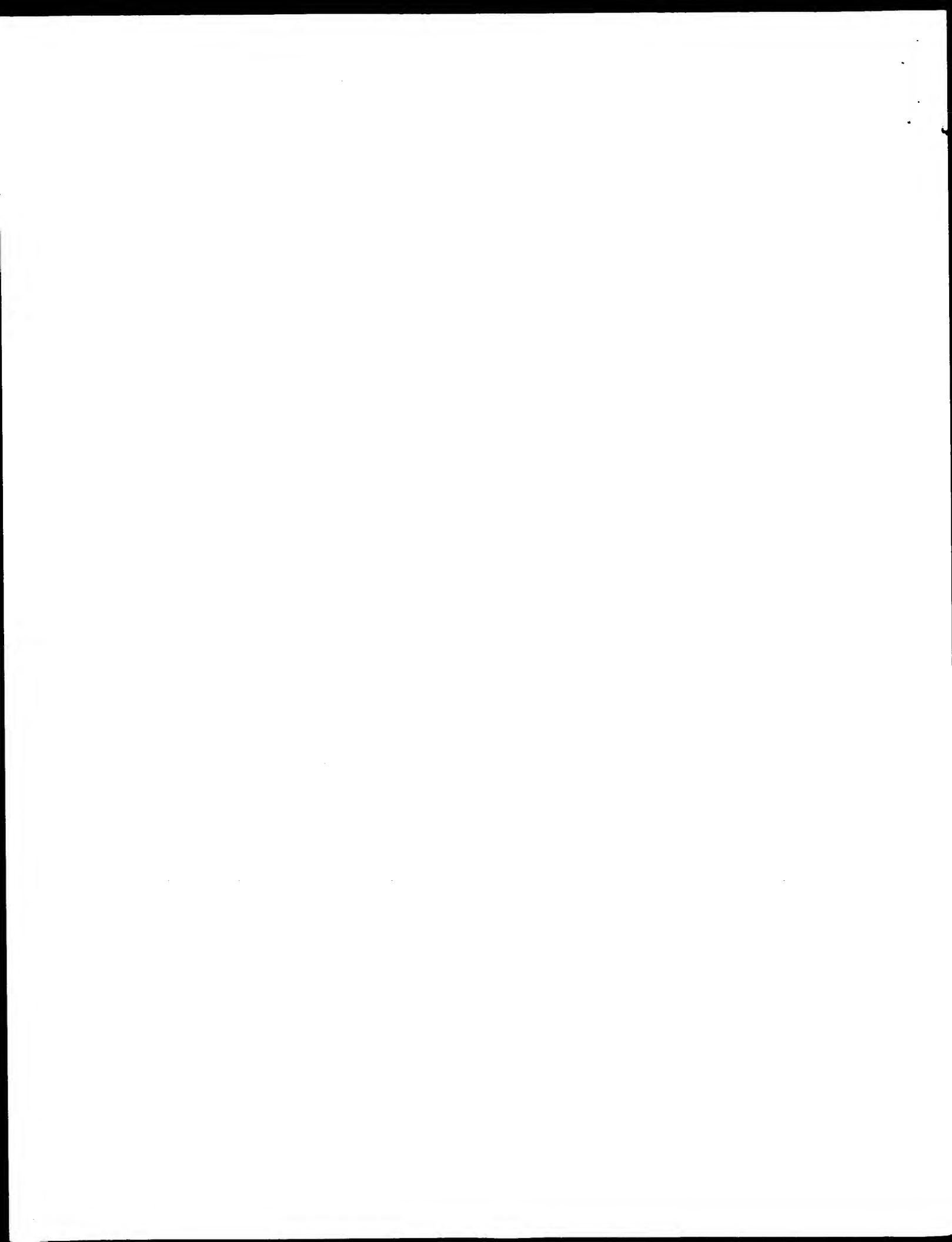


09 JULY 1999 (09.07.99)

sensitivity of the neuronal cell to L-Glutamate excitation. Based on pharmacology, sequence homology and the signal transduction pathway that they activate, the mGluRs have been subclassified into three groups. The mGluR1 and mGluR5 receptors form group I. They are coupled to hydrolysis of phosphatidylinositol (PI) and are selectively activated by (RS)-3,5-dihydroxyphenylglycine (Brabet et al., *Neuropharmacology*, 34, 895-903, 1995). Group II comprises mGluR<sub>2</sub> and mGluR<sub>3</sub> receptors. They are negatively coupled to adenylate cyclase and are selectively activated by (2S,1'R,2'R,3'R)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV; Hayashi et al., *Nature*, 366, 687-690, 1993). Finally, the mGluR<sub>4</sub>, mGluR<sub>6</sub>, mGluR<sub>7</sub> and mGluR<sub>8</sub> receptors belong to group III. They are also negatively coupled to adenylate cyclase and are selectively activated by (L)-2-amino-4-phosphonobutyric acid (L-AP4; Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426).

Agonists and antagonists of these receptors are believed useful for the treatment of acute and chronic neurodegenerative conditions, and as antipsychotic, anticonvulsant, analgesic, anxiolytic, antidepressant, and anti-emetic agents. Antagonists and agonists of neural receptors are classified as selective for a particular receptor or receptor subtype, or as non-selective. Antagonists may also be classified as competitive or non-competitive. While competitive and non-competitive antagonists act on the receptors in a different manner to produce similar results, selectivity is based upon the observations that some antagonists exhibit high levels of activity at a single receptor type, and little or no activity at other receptors. In the case of receptor-specific diseases and conditions, the selective agonists and antagonists are of the most value.

Compounds such as L-Glutamic acid, Quisqualic acid and Ibotenic acid are known to act as non-selective agonists on the mGluRs, while selective ionotropic glutamate receptor agonists such as NMDA, AMPA and Kainic acid have little effect on these receptors. Recently a few compounds without activity at the ionotropic glutamate receptors but with activity at the metabotropic receptors have been identified. These include *trans*-ACPD (*trans* (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid), the partial agonist L-AP3 (L-2-amino-3-phosphonopropionic acid, Palmer, E., Monaghan, D. T. and Cotman, C. W. *Eur. J. Pharmacol.* 166, 585-587, 1989; Desai, M. A. and Conn, P. J. *Neuroscience Lett.* 109, 157-162, 1990; Schoepp, D. D. et al., *J. Neurochemistry*, 56, 1789-1796, 1991; Schoepp D. D. and Johnson B. G. *J. Neurochemistry* 53, 1865-1869, 1989), L-AP4 (L-2-amino-4-phosphonobutyric acid) which is an agonist at the mGluR<sub>4</sub> receptor (Thomsen C. et al., *Eur. J. Pharmacol.* 227, 361-362, 1992) and some of the isomers of CCG (2-(carboxycyclopropyl)glycines) especially L-CCG-I and L-CCG-II (Hayashi, Y. et al., *Br. J. Pharmacol.* 107, 539-543, 1992).



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Very few selective antagonists at the mGluRs have been reported. However some phenylglycine derivatives, *S*-4CPG (*S*-4-carboxyphenylglycine), *S*-4C3HPG (*S*-4-carboxy -3-hydroxyphenylglycine) and *S*-MCPG (*S*- $\alpha$ -methyl-4-carboxyphenylglycine) have been reported to antagonize *trans*-ACPD- stimulated phosphoinositide hydrolysis and thus possibly act as antagonists at mGluR<sub>1</sub> and mGluR<sub>5</sub> subtypes (Thomsen, C. and Suzdak, P, *Eur. J. Pharmacol.* 245, 299, 1993).

Research directed towards mGluRs is beginning to show that mGluRs may be implicated in a number of normal as well as pathological mechanisms in the brain and spinal cord. For example, activation of these receptors on neurons can: influence levels of alertness, attention and cognition; protect nerve cells from excitotoxic damage resulting from ischemia, hypoglycemia and anoxia; modulate the level of neuronal excitation; influence central mechanisms involved in controlling movement; reduce sensitivity to pain; reduce levels of anxiety.

The use of compounds active at the mGluRs for the treatment of epilepsy is corroborated by investigations of the influence of *trans*-ACPD on the formation of convulsions (Sacaan and Schoepp, *Neuroscience Lett.* 139, 77, 1992) and that phosphoinositide hydrolysis mediated via mGluR is increased after kindling experiments in rats (Akiyama et al. *Brain Res.* 569, 71, 1992).

*Trans*-ACPD has been shown to increase release of dopamine in the rat brain, which indicates that compounds acting on the mGluRs might be usable for the treatment of Parkinson's disease and Huntington's Chorea (Sacaan et al, *J. Neurochemistry* 59, 245, 1992).

*Trans*-ACPD has also been shown to be a neuroprotective agent in a medial cerebral artery occlusion (MCAO) model in mice (Chiamulera et al. *Eur. J. Pharmacol.* 215, 353, 1992), and it has been shown to inhibit NMDA-induced neurotoxicity in nerve cell cultures (Koh et al., *Proc. Natl. Acad. Sci. USA* 88, 9431, 1991). The mGluR-active compounds are also implicated in the treatment of pain. This is proved by the fact that antagonists at the metabotropic glutamate receptors antagonize sensory synaptic response to noxious stimuli of thalamic neurons (Eaton, S. A. et al, *Eur. J. Neuroscience*, 5, 186, 1993).

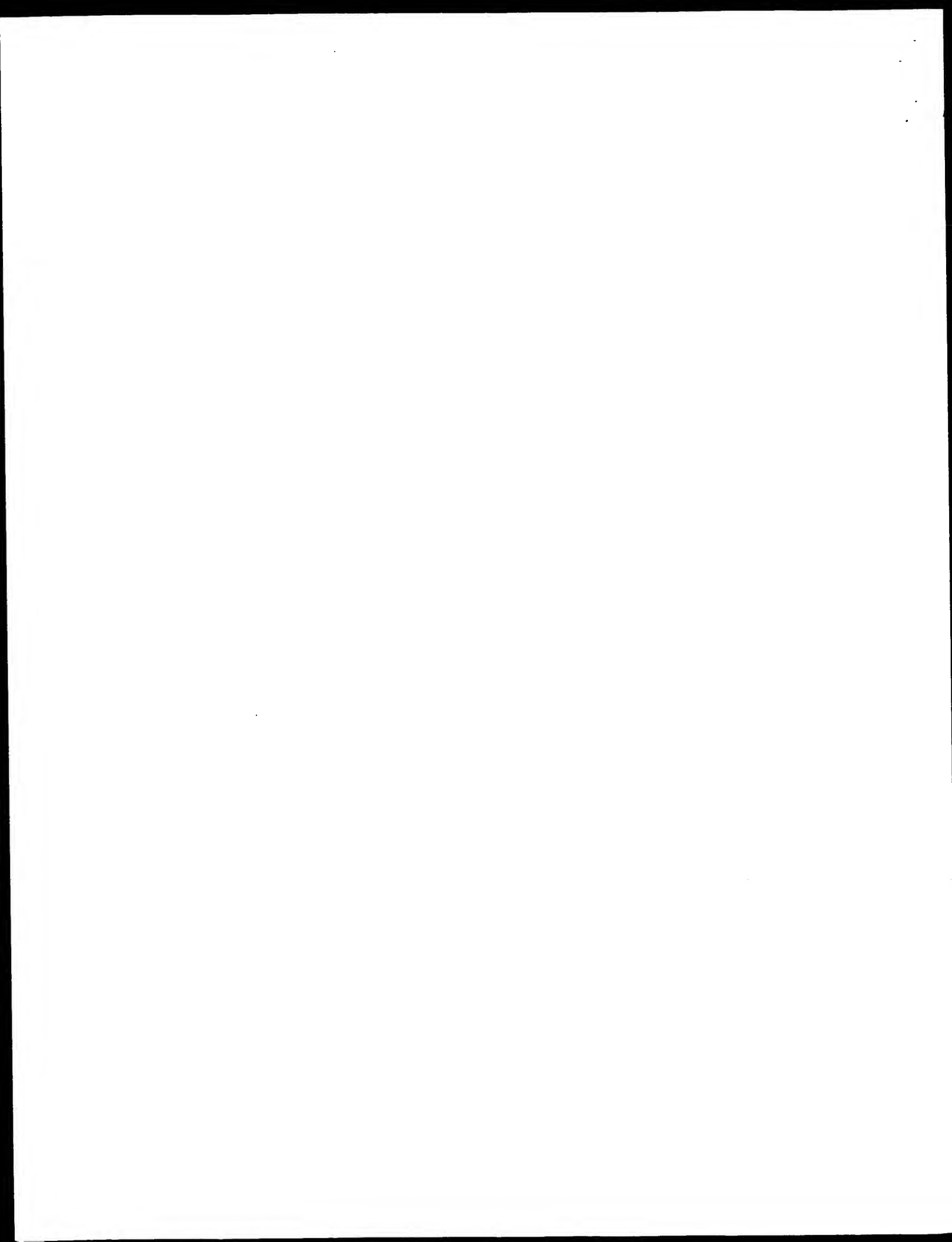
The use of compounds active at the mGluRs for treatment of neurological diseases such as senile dementia have also been indicated by the findings of Zheng and Gallagher (*Neuron* 9, 163, 1992) and Bashir et al. (*Nature* 363, 347, 1993) who demonstrated that activation of mGluRs is necessary for the induction of long-term potentiation (LTP) in nerve cells (septal nucleus, hippocampus) and the finding that long-term depression is induced after activation of metabotropic glutamate receptors in cerebellar granule cells (Linden et al. *Neuron* 7, 81, 1991).



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Thus compounds that demonstrate either activating or inhibiting activity at mGluRs have therapeutic potential for the treatment of neurological disorders. These compounds have application as new drugs to treat both acute and chronic neurological disorders, such as stroke and head injuries; epilepsy; movement disorders associated with Parkinson's disease and Huntington's chorea; pain; anxiety, AIDS dementia; and Alzheimer's disease. Since the mGluRs can influence levels of alertness, attention and cognition; protect nerve cells from excitotoxic damage resulting from ischemia, hypoglycemia and anoxia; modulate the level of neuronal excitation; influence central mechanisms involved in controlling movement; reduce sensitivity to pain; and reduce levels of anxiety, these compounds can also be used to influence these situations and also find use in learning and memory deficiencies such as senile dementia. mGluRs may also be involved in addictive behavior, alcoholism, drug addiction, sensitization and drug withdrawal (*Science*, 280:2045, 1998), so compounds acting at mGluRs might also be used to treat these disorders.

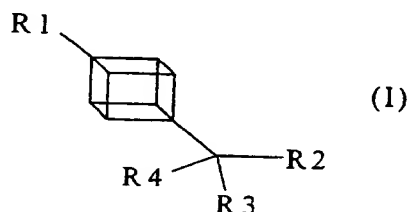
The current pharmaceutical options for treating neurological disorders tend to be very general and non-specific in their actions in that, although they may reduce the clinical symptoms associated with a specific neurological disorder, they may also negatively impact normal function of the central nervous system of patients. Thus new cellular targets and drugs that are more specific in their actions require to be identified and developed and thus a need remains for chemical compounds that demonstrate specific binding characteristics towards mGluRs.



## SUMMARY OF THE INVENTION

09 JULY 1999 (09-07-99)

It is an object of this invention to provide novel compounds that demonstrate activity at the various metabotropic glutamate receptors (mGluRs). In particular, a compound of Formula I and stereoisomers thereof:



wherein:

**R1** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfinio, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, -CH<sub>2</sub>-isoxazol and higher homologues thereof;

**R2** can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea,

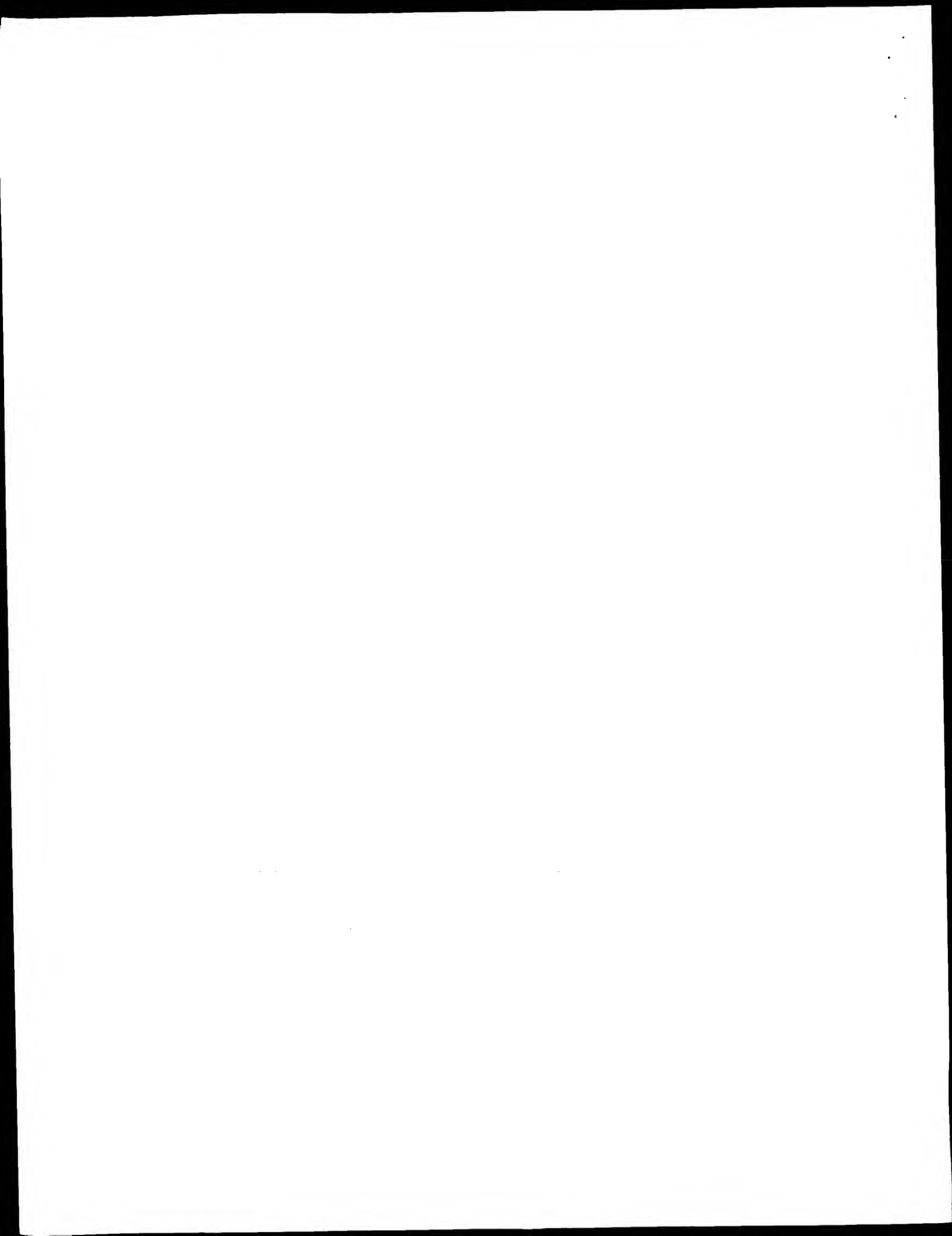
**R3** can be H, aliphatic, aromatic or heterocyclic,

**R4** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol;

and pharmaceutically acceptable salts thereof.

## DETAILED DESCRIPTION OF THE INVENTION

The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius, "N" refers to normal or normality; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "mL" means milliliter or milliliters; "M" refers to molar or molarity, "MS" refers to mass spectrometry, "IR"





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refers to infrared spectroscopy; and "NMR" refers to nuclear magnetic resonance spectroscopy.

As would be understood by the skilled artisan throughout the synthesis of the compounds of Formula I, it may be necessary to employ an amino-protecting group or a carboxy-protecting group in order to reversibly preserve a reactively susceptible amino or carboxy functionality while reacting other functional groups on the compound.

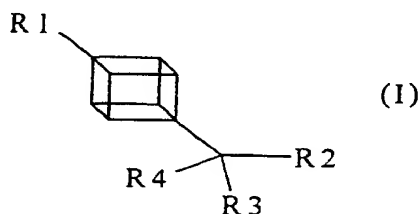
Examples of such amino-protecting groups include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, *t*-butoxycarbonyl, 2-(4-xenyl)-isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxy-carbonyl, 1-methylcyclopentanyloxy-carbonyl, cyclohexanyloxy-carbonyl, 1-methylcyclohexanyloxy-carbonyl, 2-methylcyclohexanyloxy-carbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)-ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; benzoylmethylsulfonyl group, 2-nitrophenylsulfonyl, diphenylphosphine oxide and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino-protecting group(s). Preferred amino-protecting groups are *t*-butoxycarbonyl (*t*-Boc), allyloxycarbonyl and benzyloxycarbonyl (CbZ). Further examples of these groups are found in E. Haslam in *Protective Groups in Organic Synthesis*; McOmie, J. G. W., Ed. 1973, at Chapter 2; and Greene, T.W. and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, Second edition; Wiley-Interscience: 1991; Chapter 7.

Examples of such carboxyl-protecting groups include methyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, *t*-butyl, *t*-amyl, trityl,



4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4''-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, *t*-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl,  $\beta$ -(di(*n*-butyl)methylsilyl)ethyl, *p*-toluenesulfonoethyl, 4-nitrobenzylsulfonoethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl and like moieties. Preferred carboxyl-protecting groups are allyl, benzyl and *t*-butyl. Further examples of these groups are found in E. Haslam, *supra*, at Chapter 5; and T. W. Greene and P. G. M. Wuts, *supra*, at Chapter 5.

The present invention provides a compound of the formula:



wherein:

**R1** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfinio, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, -CH<sub>2</sub>-isoxazol and higher analogues thereof;

**R2** can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourea ;

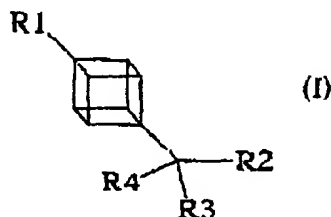
**R3** can be H, aliphatic, aromatic or heterocyclic;

**R4** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol;

and pharmaceutically acceptable salts thereof.



In particular compounds wherein the compound of Formula I is selected from the group consisting of:



wherein:

**R1** is COOH

**R2** is NH<sub>2</sub>

**R3** can be H or methyl or xanthyl or thioxanthyl or -CH<sub>2</sub>-xanthyl or -CH<sub>2</sub>-thioxanthyl and

**R4** is COOH

While all of the compounds of Formula I are believed to demonstrate activity at the metabotropic glutamate receptors (mGluRs), certain groups of Formula I compounds are more preferred for such use.

As noted above, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic



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acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid

Salts of amine groups may also comprise quarternary ammonium salts in which the amino nitrogen carries a suitable organic group such as an alkyl, alkenyl, alkynyl, or aralkyl moiety.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. This invention further encompasses the pharmaceutically acceptable solvates of the compounds of Formula I. Many of the Formula I compounds can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

The compounds of the present invention have multiple asymmetric (chiral) centers. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of

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diastereomers. All asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

The prefixes "R" and "S" are used herein as commonly used in organic chemistry to denote the absolute configuration of a chiral center, according to the Cahn-Ingold-Prelog system. The stereochemical descriptor *R* (*rectus*) refers to that configuration of a chiral center with a clockwise relationship of groups tracing the path from highest to second-lowest priorities when viewed from the side opposite to that of the lowest priority group. The stereochemical descriptor *S* (*sinister*) refers to that configuration of a chiral center with a counterclockwise relationship of groups tracing the path from highest to second-lowest priority when viewed from the side opposite to the lowest priority group. The priority of groups is decided using sequence rules as described by Cahn et al., *Angew. Chem.*, 78, 413-447, 1966 and Prelog, V. and Helmchen, G, *Angew. Chem. Int. Ed. Eng.*, 21, 567-583, 1982).

In addition to the *R,S* system used to designate the absolute configuration of a chiral center, the older D-L system is also used in this document to denote relative configuration, especially with reference to amino acids and amino acid derivatives. In this system a Fischer projection of the compound is oriented so that carbon-1 of the parent chain is at the top. The prefix "D" is used to represent the relative configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and "L", that of the isomer in which it is on the left.

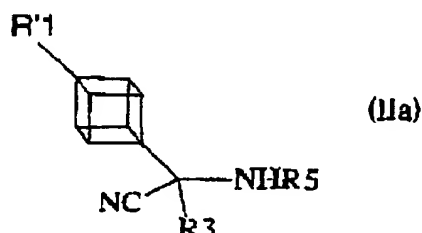
As would be expected, the stereochemistry of the Formula I compounds is critical to their potency as agonists or antagonists. The relative stereochemistry is established early during synthesis, which avoids subsequent stereoisomer separation problems later in the process. Further manipulation of the molecules then employs stereospecific procedures so as to maintain the preferred chirality. The preferred methods of this invention are the methods employing those preferred compounds.

Non-toxic metabolically-labile esters and amides of compounds of Formula I are ester or amide derivatives of compounds of Formula I that are hydrolyzed in vivo to afford said compounds of Formula I and a pharmaceutically acceptable alcohol or amine. Examples of metabolically-labile esters include esters formed with (1-6C) alkanols in which the alkanol moiety may be optionally substituted by a (1-8C) alkoxy group, for example methanol, ethanol, propanol and methoxyethanol. Examples of metabolically-labile amides include amides formed with amines such as methylamine.



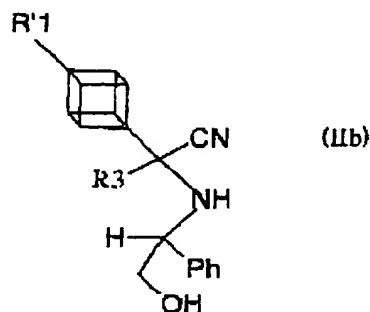
According to another aspect, the present invention provides a process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:

(a) hydrolyzing a compound of formula (IIa):



wherein: **R'1** is an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfonyl, sulfinyl, boronyl, tetrazol, isoxazol,  $-\text{CH}_2\text{-carboxyl}$ ,  $-\text{CH}_2\text{-phosphono}$ ,  $-\text{CH}_2\text{-phosphino}$ ,  $-\text{CH}_2\text{-sulfonyl}$ ,  $-\text{CH}_2\text{-sulfinyl}$ ,  $-\text{CH}_2\text{-boronyl}$ ,  $-\text{CH}_2\text{-tetrazol}$ ,  $\text{CH}_2\text{-isoxazol}$  and higher analogues thereof, or a protected form thereof, **R3** can be H, aliphatic, aromatic or heterocyclic and **R5** represents a hydrogen atom or an acyl group. Preferred values for **R5** are hydrogen and (2-6C) alkanoyl groups, such as acetyl; or

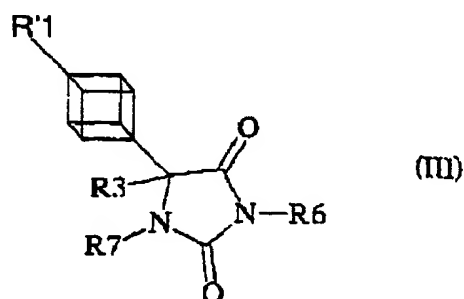
(b) deprotecting and hydrolyzing a compound of formula (IIb)



wherein: **R'1** and **R3** are as defined above; or



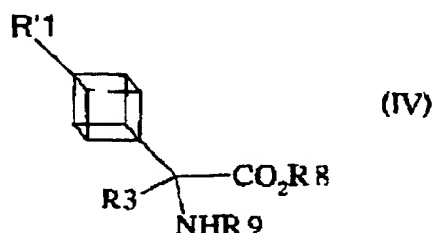
(c) hydrolyzing a compound of formula:



wherein: **R'1** and **R3** has the meaning defined above, **R6** and **R7** each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof; or



(d) deprotecting a compound of formula:



wherein: **R'1** and **R3** has the meaning defined above, **R8** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R9** represents a hydrogen atom or a nitrogen protecting group;

whereafter, if necessary and/or desired:

- (i) resolving the compound of Formula I;
- (ii) converting the compound of Formula I into a non-toxic metabolically-labile ester or amide thereof;
- and/or;
- (iii) converting the compound of Formula I or a non-toxic metabolically-labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

The protection of carboxylic acid and amino groups is generally described in McOmie, *Protecting Groups in Organic Chemistry*, Plenum Press, NY, 1973, and Greene and Wuts, *Protecting Groups in Organic Synthesis*, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxyl protecting groups include alkyl groups such as methyl, ethyl, *t*-butyl and *t*-amyl; aralkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and triyl; silyl groups such as trimethylsilyl and *t*-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine-protecting groups include acyl groups, such as groups of formula **R9** CO in which **R9** represents (1-6C) alkyl, (3-10C) cycloalkyl, phenyl(1-6C) alkyl, phenyl(1-6C) alkoxy, or a (3-10C) cycloalkoxy, wherein a phenyl group may optionally be substituted by one or two





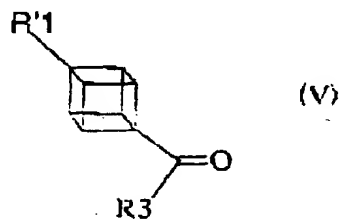
substituents independently selected from amino, hydroxy, nitro, halogeno, (1-6C) alkyl, (1-6C) alkoxy, carboxyl, (1-6C) alkoxycarbonyl, carbamoyl, (1-6C) alkanoylamino, (1-6C) alkylsulphonylamino, phenylsulphonylamino, toluenesulphonylamino, and (1-6C) fluoroalkyl.

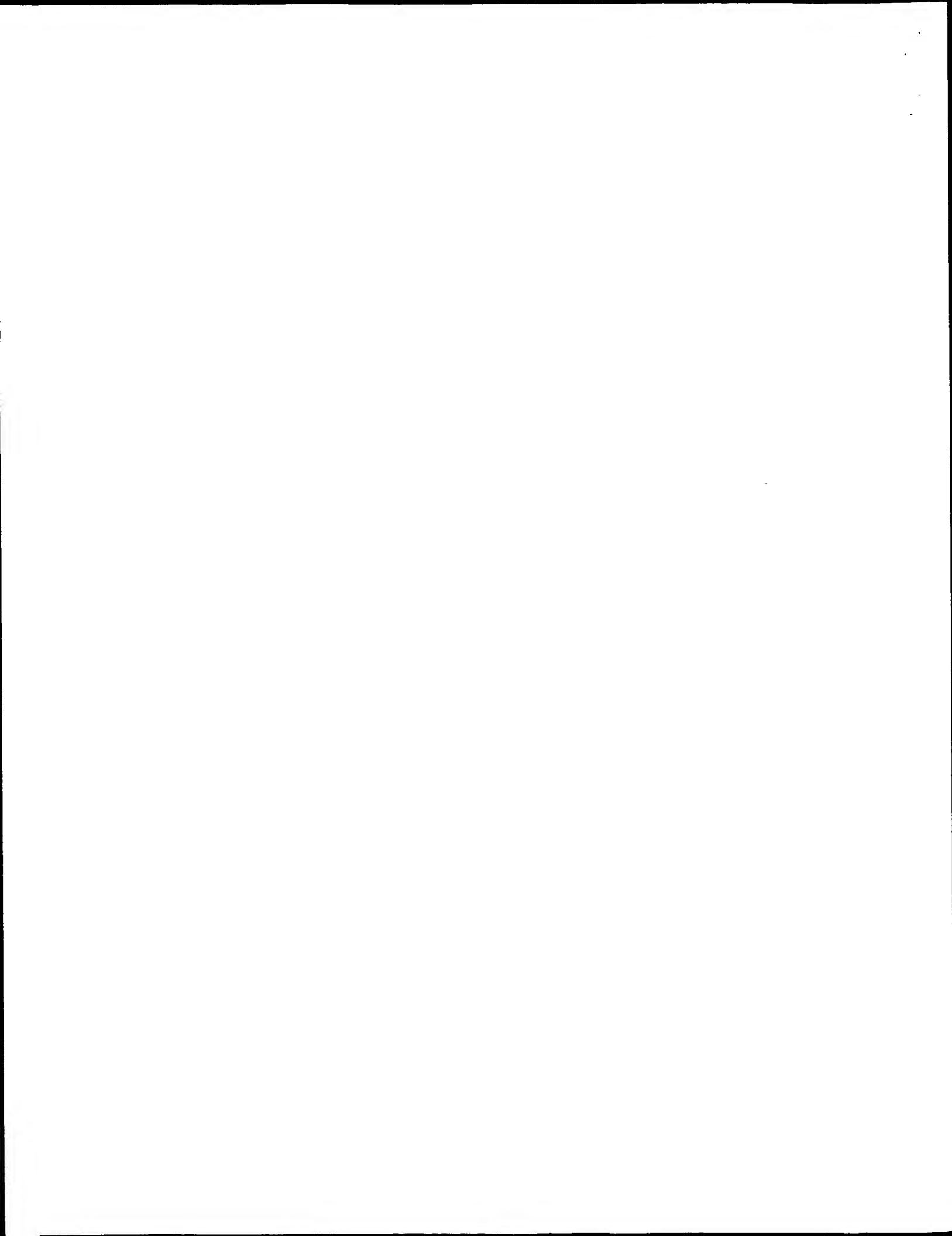
The compounds of Formula II are conveniently hydrolyzed in the presence of an acid, such as hydrochloric acid or sulfuric acid, or a base, such as an alkali metal hydroxide, for example sodium hydroxide. The hydrolysis is conveniently performed in an aqueous solvent such as water and at a temperature in the range of 50 to 200 °C.

The compounds of Formula III are conveniently hydrolyzed in the presence of a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline earth metal hydroxide such as barium hydroxide. Suitable reaction media include water. The temperature is conveniently in the range of from 50 to 150 °C.

The compounds of Formula IV may be deprotected by a conventional method. Thus, an alkyl carboxyl protecting group may be removed by hydrolysis. The hydrolysis may conveniently be performed by heating the compound of Formula IV in the presence of either a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline metal hydroxide, such as barium hydroxide, or an acid such as hydrochloric acid. The hydrolysis is conveniently performed at a temperature in the range from 10 to 300 °C. An aralkyl carboxyl protecting group may conveniently be removed by hydrogenolysis. The hydrogenolysis may conveniently be effected by reacting the compound of Formula IV with hydrogen in the presence of a Group VIII metal catalyst, for example a palladium catalyst such as palladium on charcoal. Suitable solvents for the reaction include alcohols such as ethanol. The reaction is conveniently performed at a temperature in the range from 0 to 100 °C. An acyl, amine protecting group is also conveniently removed by hydrolysis, for example as described for the removal of an alkyl carboxyl protecting group.

The compounds of Formula II may be prepared by reacting a compound of formula (V):



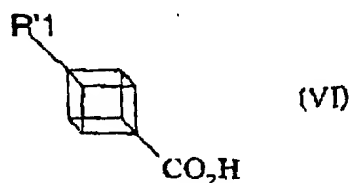


with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and an ammonium halide, such as ammonium chloride, conveniently in the presence of ultrasound. Thus, the ammonium halide is mixed with chromatography grade alumina in the presence of a suitable diluent such as acetonitrile. The mixture is then irradiated with ultrasound, whereafter the compound of Formula V is added, and the mixture is again irradiated. The alkali metal cyanide is then added, followed by further irradiation with ultrasound.

Individual isomers of compounds of Formula I may be made by reacting a compound of the Formula V with the stereoisomers of the chiral agent (*S*)- and (*R*)-phenylglycinol and a reactive cyanide such as trimethylsilyl cyanide.

The compounds of Formula III may be prepared by reacting a compound of Formula V with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and ammonium carbonate or ammonium carbamate. Convenient solvents include water, dilute ammonium hydroxide, alcohols such as methanol, aqueous methanol and aqueous ethanol. Conveniently the reaction is performed at a temperature in the range of from 10 to 150 °C. If desired, the compounds of Formula III may then be alkylated, for example using an appropriate compound of formula **R6 Cl** and/or **R7 Cl**.

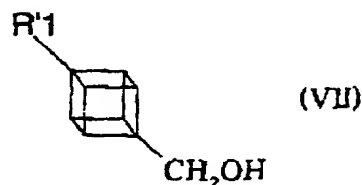
The compounds of Formula V can be prepared by reacting a compound of formula:



with a chlorinating agent such as thionyl chloride or phosphorous (V) chloride, followed by reaction with organo copper or organo metal or Grignard reagent derived from **R3 X** or by reaction with ethyl hydrogen malonate in the presence of organolithium, wherein **R3** has the meaning defined above and **X** is halogen.

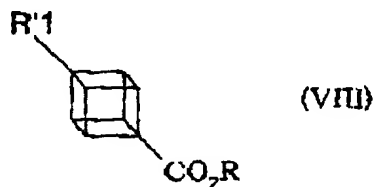


The compounds of Formula V can also be prepared by oxidizing a compound of formula



under Swern conditions.

The compounds of Formula VI can be prepared from compounds of formula:



by reduction.

When R'1 is CO<sub>2</sub>Me, this compound can be bought commercially. When R'1 is another substituent, the compound of Formula VIII can be made using standard procedures.

Many of the intermediates described herein, for example the compounds of Formula II, III and IV are believed to be novel, and are provided as further aspects of the invention.

The Formula I compounds of the present invention are agonists or antagonists at certain metabotropic excitatory amino acid receptors (mGluRs). Therefore, another aspect of the present invention is a method of affecting mGluRs in mammals, which comprises administering to a mammal requiring modulated excitatory amino acid neurotransmission a pharmacologically-effective amount of a compound of Formula I. The term "pharmacologically-effective amount" is used to represent an amount of the compound of the invention that is capable of affecting the mGluRs. By affecting, a compound of the invention is acting as an agonist or antagonist. When a compound of the



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invention acts as an agonist, the interaction of the compound with the excitatory amino acid receptor mimics the response of the interaction of this receptor with its natural ligand (i.e. L-Glutamic acid). When a compound of the invention acts as an antagonist, the interaction of the compound with the excitatory amino acid receptor blocks the response of the interaction of this receptor with its natural ligand (i.e. L-Glutamic acid).

The particular dose of compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the compound may be administered by continuous infusion. A typical daily dose will contain from about 0.001 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 20 mg/kg.

A variety of physiological functions have been shown to be subject to influence by excessive or inappropriate stimulation of excitatory amino acid transmission. The Formula I compounds of the present invention are believed (through their interactions at the mGluRs) to have the ability to treat a variety of neurological disorders in mammals associated with this condition, including acute neurological disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia (e.g. stroke and cardiac arrest), spinal cord trauma, head trauma, perinatal hypoxia, and hypoglycemic neuronal damage. The Formula I compounds are believed to have the ability to treat a variety of chronic neurological disorders, such as Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage and retinopathy, cognitive disorders, and idiopathic and drug-induced Parkinson's disease. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of Formula I.

The Formula I compounds of the present invention (through their interactions at the mGluRs) are also believed to have the ability to treat a variety of other neurological disorders in mammals that are associated with glutamate dysfunction, including muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, anxiety and related disorders (e.g. panic attack), emesis, brain edema, chronic pain, sleep disorders, Tourette's syndrome, attention





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deficit disorder, and tardive dyskinesia. Therefore, the present invention also provides methods for treating these disorders which comprise administering to a patient in need thereof an effective amount of the compound of Formula I.

The Formula I compounds of the present invention (through their interactions at the mGluRs) are also believed to have the ability to treat a variety of psychiatric disorders, such as schizophrenia, anxiety and related disorders (e.g. panic attack), depression, bipolar disorders, psychosis, and obsessive compulsive disorders. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of Formula I.

The pharmacological properties of the compounds of the invention can be illustrated by determining their effects in various functional in vitro assays. The compounds of the invention were studied in an in vitro assay that measured the inhibition of PI hydrolysis or the formation of cyclic AMP in Chinese hamster ovary cell lines expressing mGluR<sub>1α</sub>, mGluR<sub>2</sub> and mGluR<sub>4</sub>, cloned metabotropic glutamate receptors.

### Principle

So far eight different clones of the G-protein-coupled mGluRs have been identified (Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426). These receptors function to modulate the presynaptic release of L-Glutamate, and the postsynaptic sensitivity of the neuronal cell to L-Glutamate excitation. Based on pharmacology, sequence homology and the signal transduction pathway that they activate, the mGluRs have been subclassified into three groups. The mGluR<sub>1</sub> and mGluR<sub>5</sub> receptors form group I. They are coupled to hydrolysis of phosphatidylinositol (PI) and are selectively activated by (RS)-3,5-dihydroxyphenylglycine (Brabet et al., *Neuropharmacology*, 34, 895-903, 1995). Group II comprises mGluR<sub>2</sub> and mGluR<sub>3</sub> receptors. They are negatively coupled to adenylate cyclase and are selectively activated by (2S,1'R,2'R,3'R)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV; Hayashi et al., *Nature*, 366, 687-690, 1993). Finally, the mGluR<sub>4</sub>, mGluR<sub>6</sub>, mGluR<sub>7</sub> and mGluR<sub>8</sub> receptors belong to group III. They are also negatively coupled to adenylate cyclase and are selectively activated by (S)-2-amino-4-phosphonylbutyric acid (L-AP4; Knopfel et al., 1995, *J. Med. Chem.*, 38, 1417-1426).



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### Cell Culture

The Chinese hamster ovary cell lines expressing mGluR<sub>1a</sub>, mGluR<sub>2</sub> and mGluR<sub>4a</sub> receptors have been described previously (Aramori and Nakanishi, *Neuron* 8, 757-765; 1992; Tanabe et al., *Neuron* 8, 169-179, 1992; Tanabe et al., *J. Neurosci.* 13, 1372-1378). They were maintained at 37°C in a humidified 5% CO<sub>2</sub> incubator in Dulbecco's Modified Eagle Medium (DMEM) containing a reduced concentration of (S)-glutamine (2mM) and were supplemented with 1% proline, penicillin (100 U/ml), streptomycin (100 mg/ml) and 10% dialyzed fetal calf serum (all GIBCO, Paisley). Two days before assay  $1.8 \times 10^6$  cells were divided into the wells of 24 well plates.

### Second Messenger Assays

PI hydrolysis was measured as described previously (Hayashi et al., *Br. J. Pharmacol.* 107, 539-543, 1992; Hayashi et al., *J. Neurosci.* 14, 3370-3377, 1994). Briefly, the cells were labeled with [<sup>3</sup>H]inositol (2 µCi/ml) 24 h prior to the assay. For agonist assays, the cells were incubated with ligand dissolved in phosphate-buffered saline (PBS)-LiCl for 20 min, and agonist activity was determined by measurement of the level of <sup>3</sup>H-labeled mono-, bis- and tris-inositol phosphates by ion-exchange chromatography. For antagonist assays, the cells were preincubated with the ligand dissolved in PBS-LiCl for 20 min prior to incubation with ligand and 10 µM (L)-Glutamic acid for 20 min. The antagonist activity was then determined as the inhibitory effect of the (L)-Glutamic acid-mediated response. The assay of cyclic AMP formation was performed as described previously (Hayashi et al., *Br. J. Pharmacol.* 107, 539-543, 1992; Hayashi et al., *J. Neurosci.* 14, 3370-3377, 1994). Briefly, the cells were incubated for 10 min in PBS containing the ligand and 10 µM forskolin and 1mM 3-Isobutyl-1-methyxanthine (IBMX; both Sigma, St. Louis, MO, USA). The agonist activity was then determined as the inhibitory effect of the forskolin-induced cyclic AMP formation. For antagonist assay, the cells were preincubated with ligand dissolved in PBS containing 1 mM IBMX for 20 min prior to a 10 min incubation in PBS containing the ligand, 20 µM (mGluR<sub>2</sub>) or 50 µM (mGluR<sub>4a</sub>), (L)-Glutamic acid, 10 µM Forskolin and 1 mM IBMX.

### Results

Some of the compounds of the invention were tested for antagonist activity against Chinese hamster



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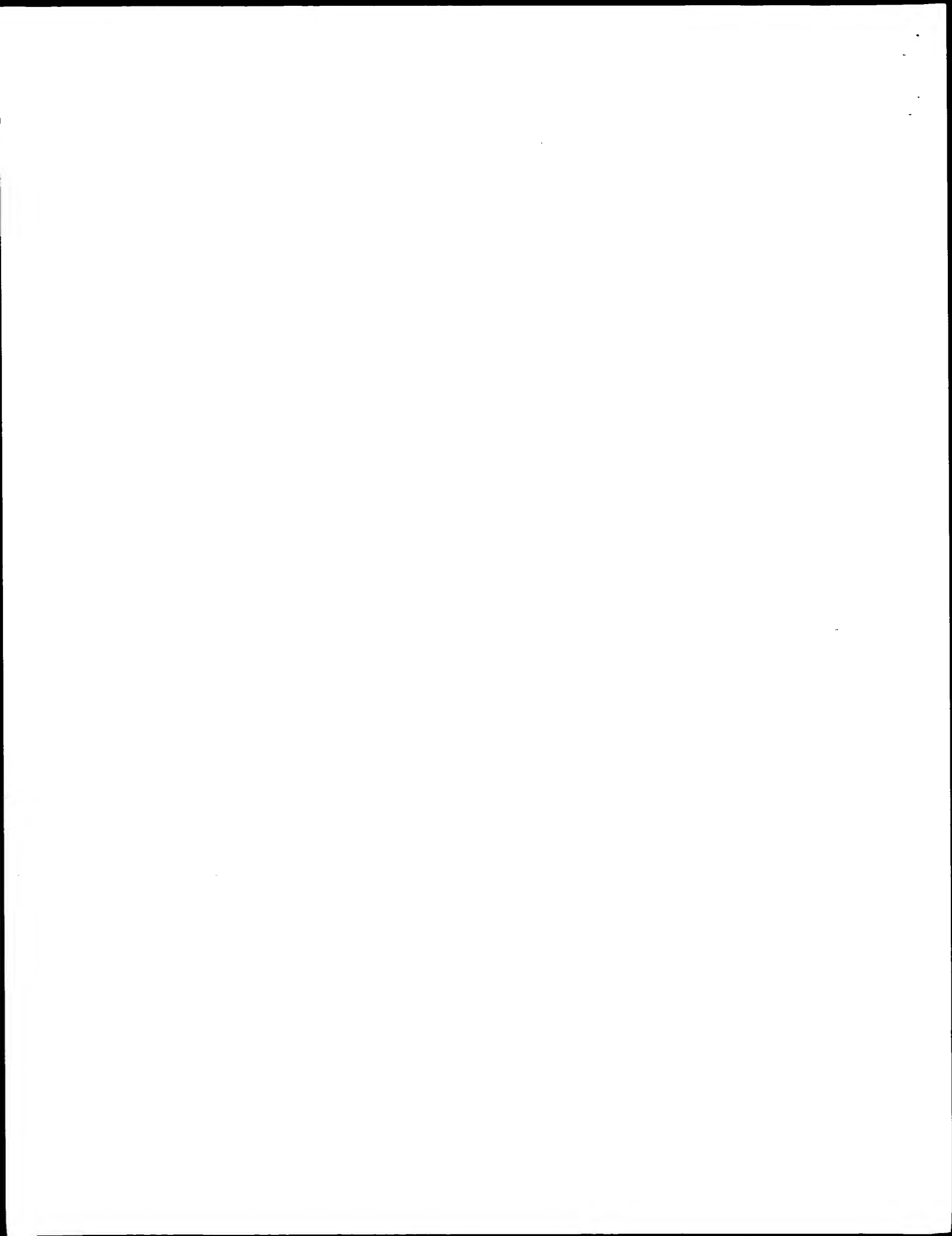
ovary cell lines expressing mGluR<sub>1α</sub>, mGluR<sub>2</sub> and mGluR<sub>4</sub>, cloned mGluRs at a concentration of 1 mM. When tested as antagonists of the increase in PI hydrolysis evoked by 10 μM (L)-Glutamic acid, some compounds of the invention effectively blocked this increase in PI hydrolysis by an action at the mGluR<sub>1α</sub> receptor. The data for one of the compounds of the invention is shown in Figure 1 below.

According to another aspect, the present invention provides a method of modulating one or more metabotropic glutamate receptor functions in a warm-blooded mammal which comprises administering an effective amount of a compound of Formula I, or a non-toxic metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof.

The compounds of the present invention are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical formulation comprising a compound of Formula I and a pharmaceutically-acceptable carrier, diluent, or excipient. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active ingredient.

The compounds of Formula I are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

The present invention also provides pharmaceutical compositions containing compounds as disclosed in the claims in combination with one or more pharmaceutically acceptable, inert or physiologically active, diluent or adjuvant. The compounds of the invention can be freeze-dried and, if desired, combined with other pharmaceutically acceptable excipients to prepare formulations for administration. These compositions may be presented in any form appropriate for the administration route envisaged. The parenteral and the intravenous route are the preferential routes for administration.



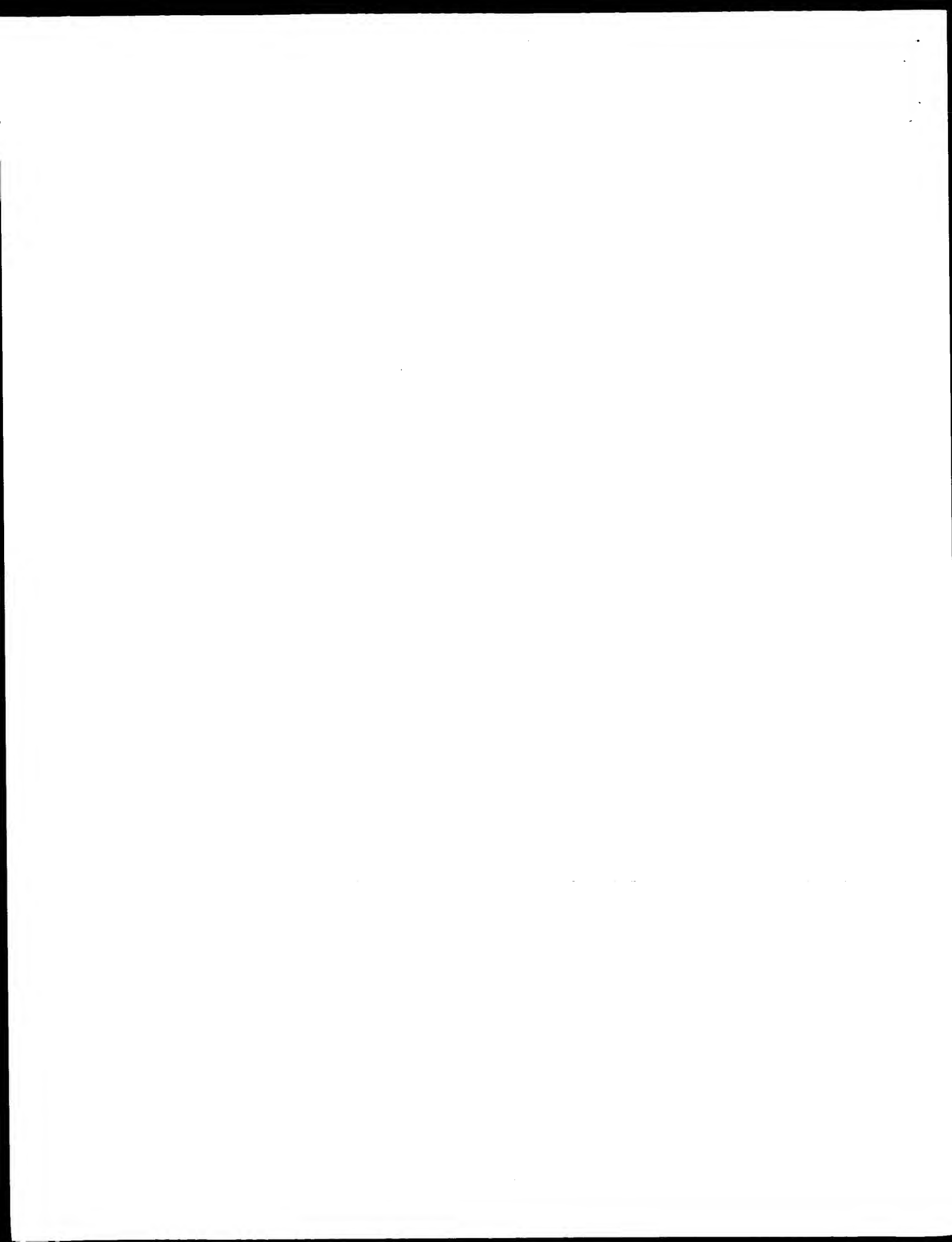
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Compounds of the general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin; or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium





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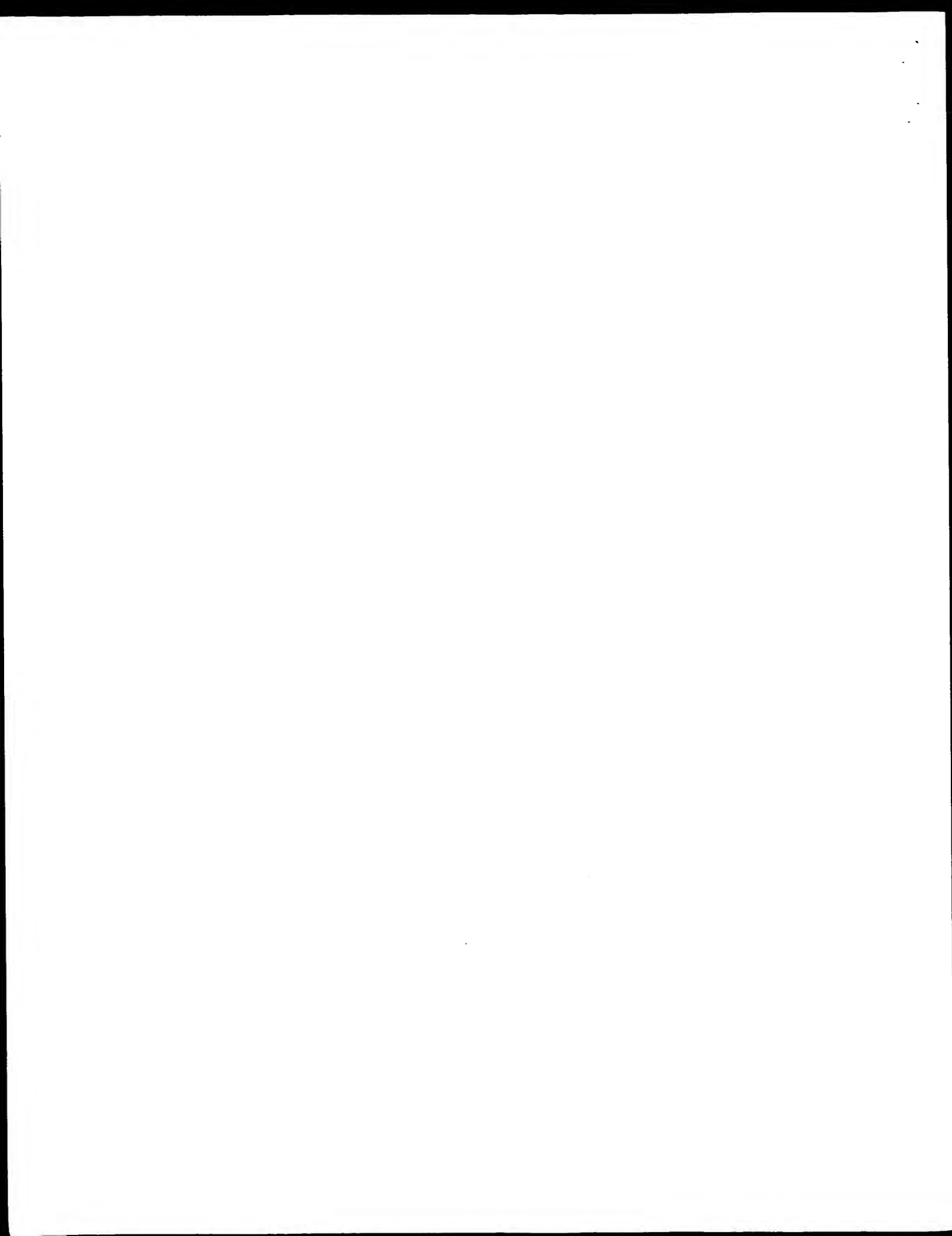
carboxymethylcellulose, methyl cellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia: dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example hepta-decaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl-*p*-hydroxy benzoate, one or more colouring agents, one or more flavouring agents or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example peanut oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin.

The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or peanut oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents



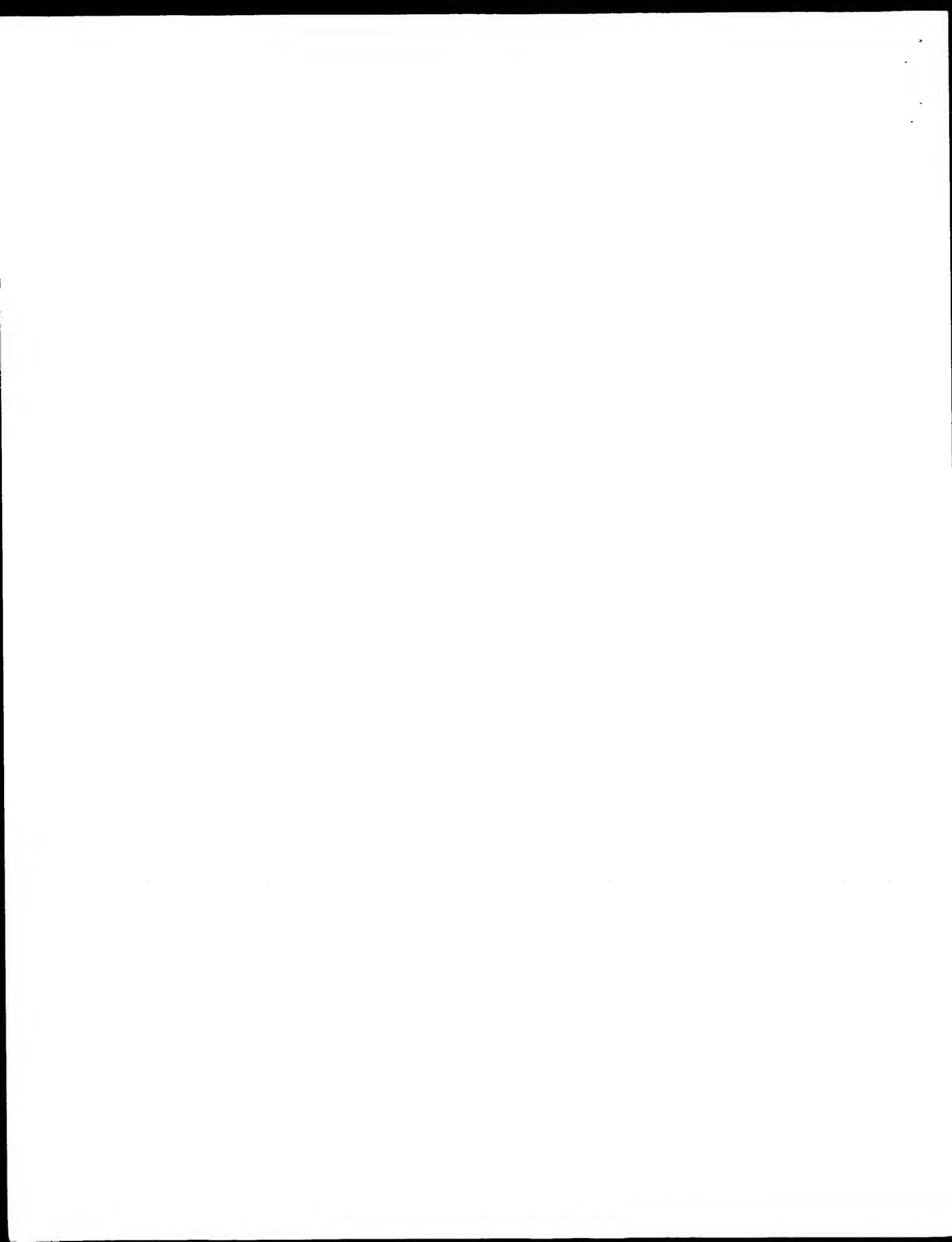
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Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or a suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compound(s) of the general Formula I may be administered, together or separately, in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compound(s) of general Formula I may be administered, together or separately, parenterally in sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

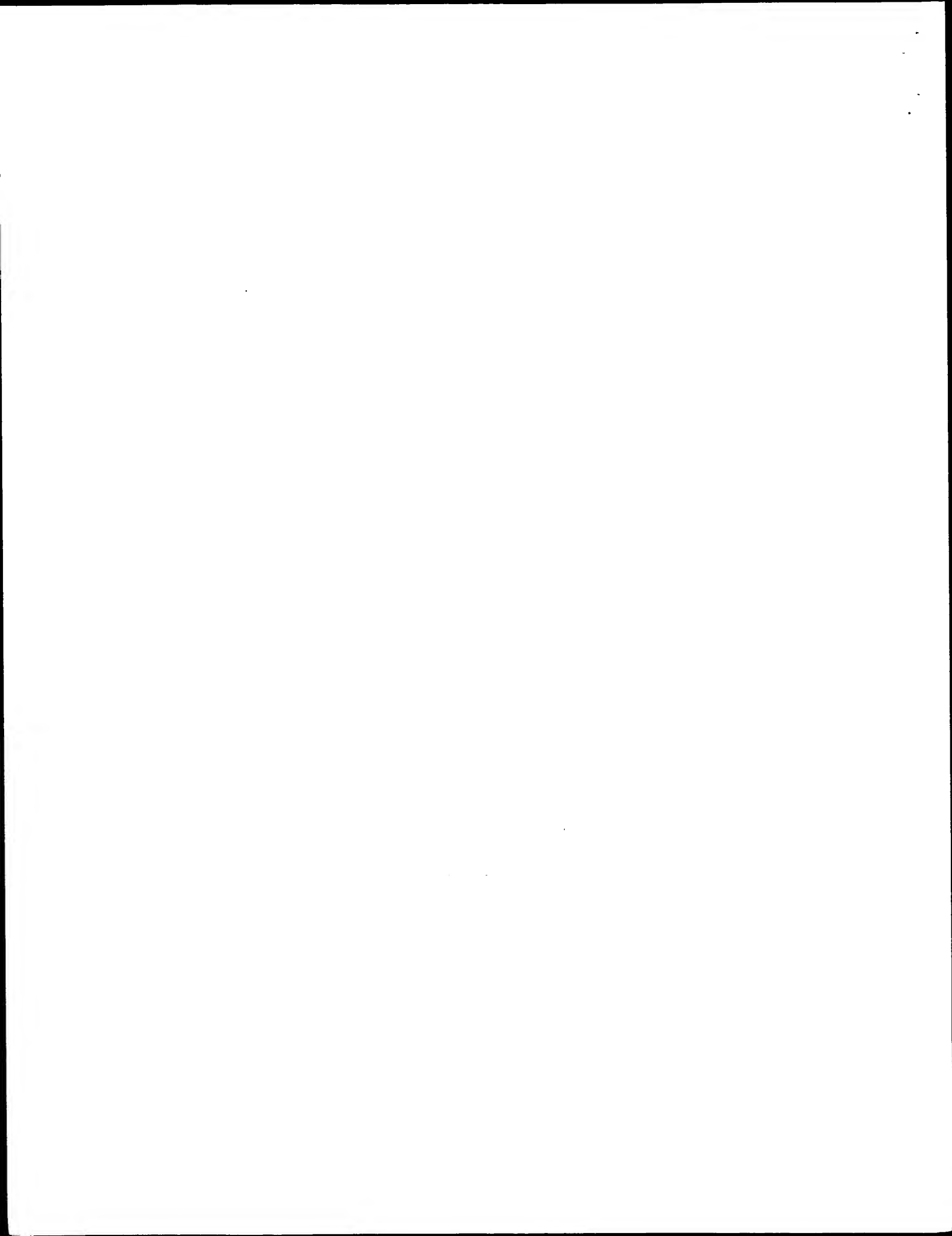
The dosage to be administered is not subject to defined limits, but it will usually be an effective amount. It will usually be the equivalent, on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active free drug to achieve its desired pharmacological and physiological effects. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.



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The active compound is effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.01 to about 30 mg/kg of body weight. A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 mg to about 500 mg, more preferably about 25 mg to about 300 mg of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.



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**Formulation 1**

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities

**Formulation 2**

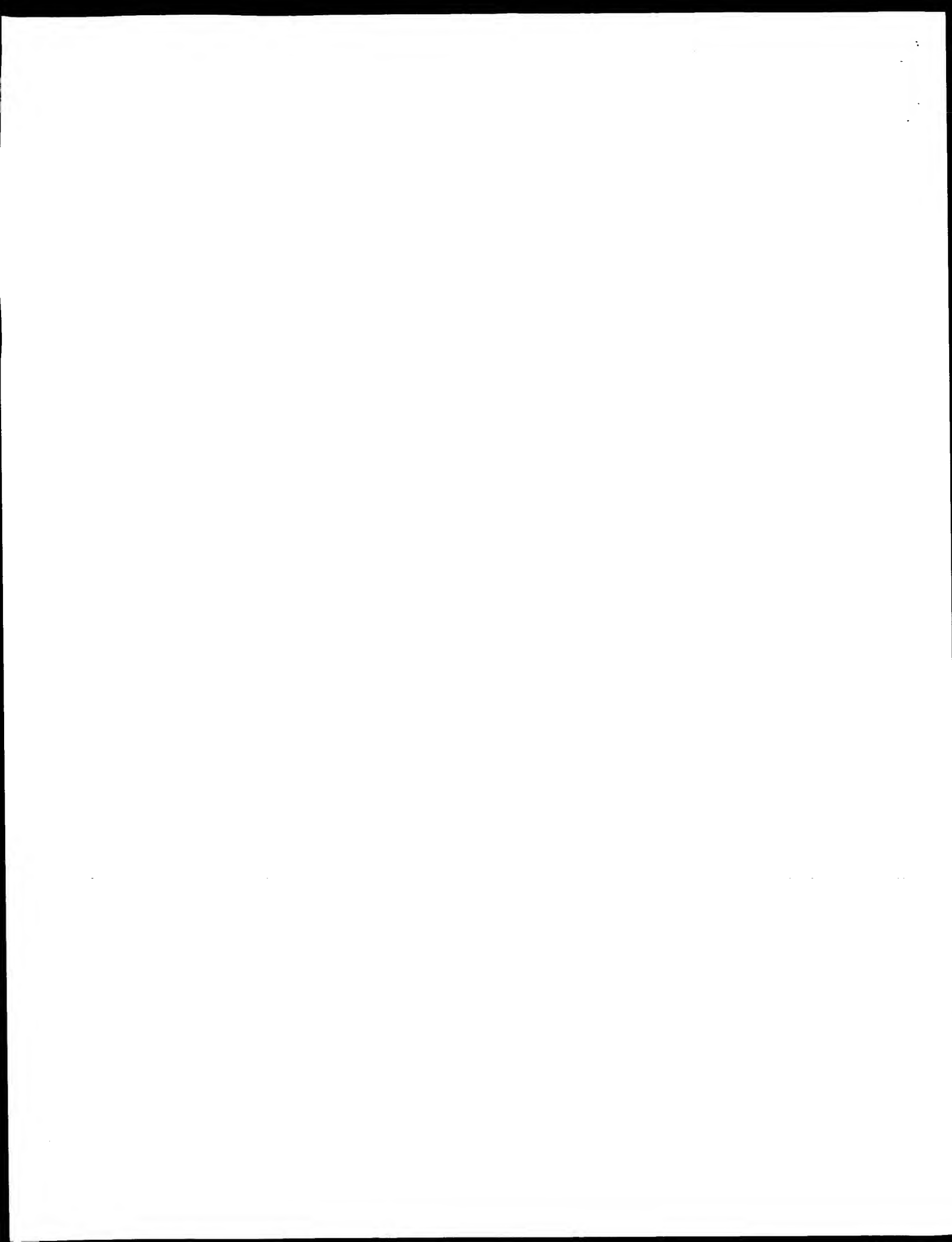
A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665

The components are blended and compressed to form tablets each weighing 665 mg.

**Formulation 3**

An aerosol solution is prepared containing the following components:





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Weight %

Active Ingredient	0.25
Ethanol	29.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	100

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30 °C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

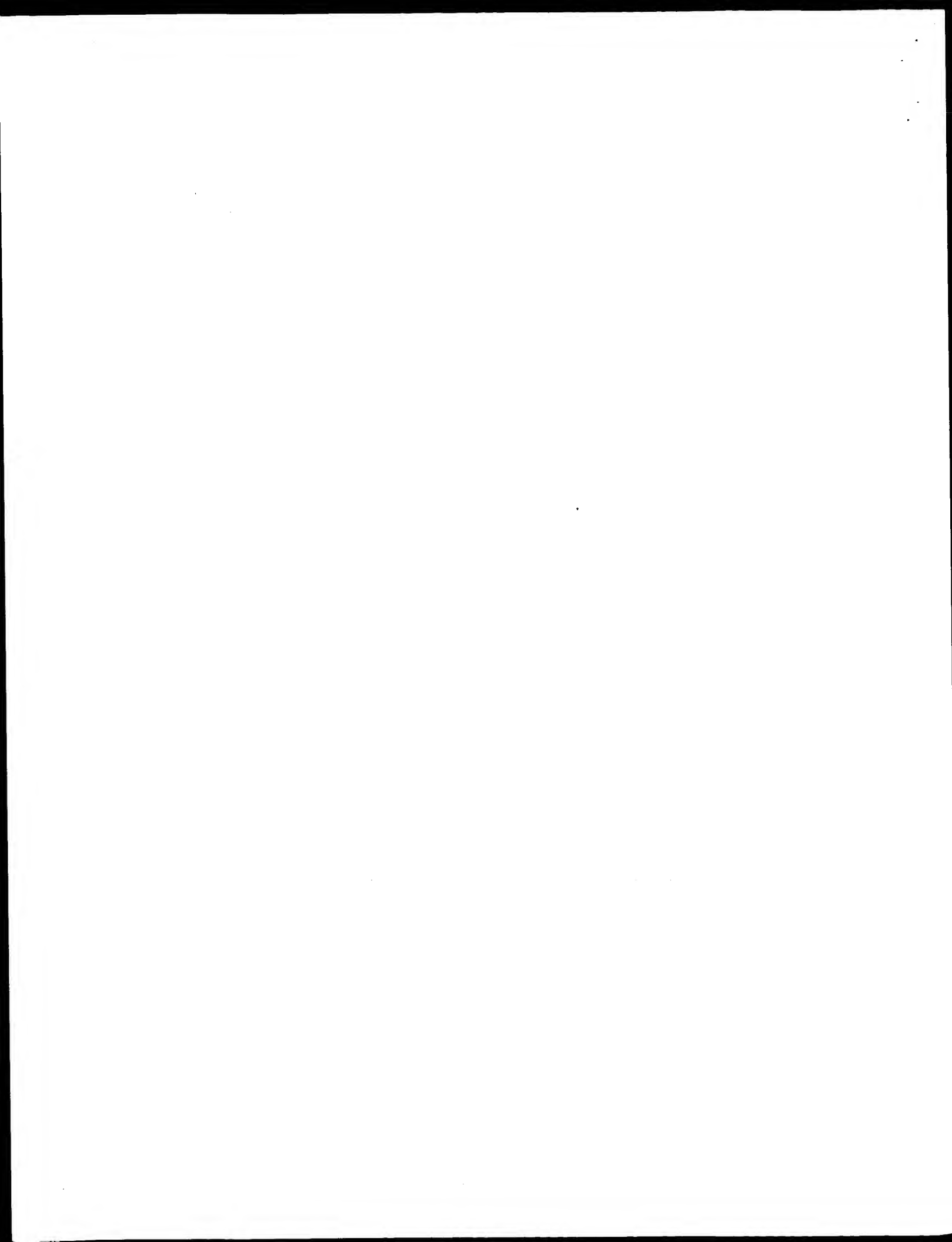
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#### *Formulation 4*

Tablets each containing 60 mg of active ingredient are made as follows:

	Quantity (mg/tablet)
Active Ingredient	60
Starch	45
Microcrystalline cellulose	35
Polyvinylpyrrolidone	4
Sodium carboxymethyl starch	4.5
Magnesium stearate	0.5
Talc	1.0
Total	150

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders that are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed



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through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

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#### *Formulation 5*

Capsules each containing 80 mg medicament are made as follows:

	Quantity (mg/capsule)
Active Ingredient	80
Starch	59
Microcrystalline cellulose	59
Magnesium stearate	2
Total	200

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 sieve, and filled into hard gelatin capsules in 200 mg quantities.

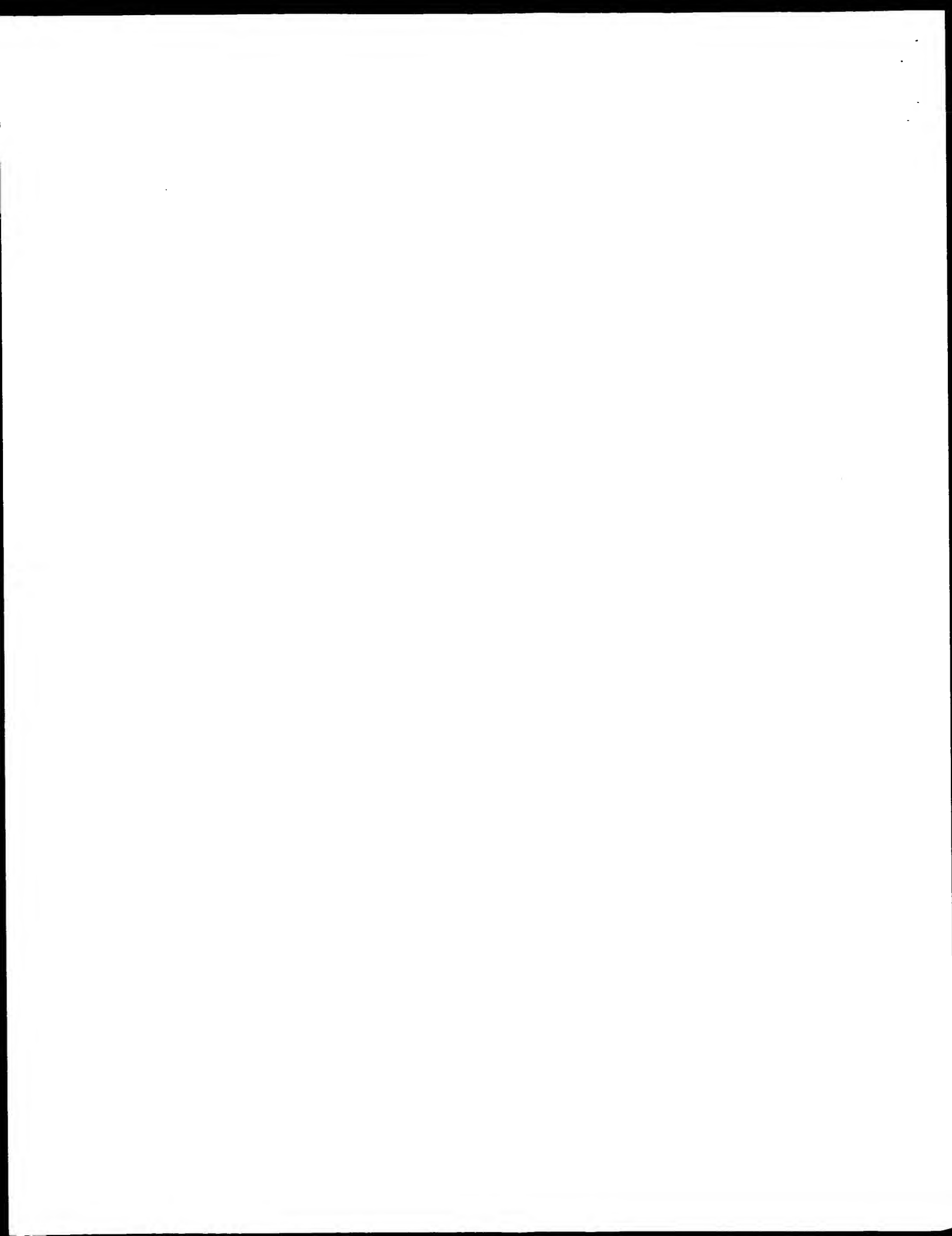
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#### *Formulation 6*

Suppositories each containing 225 mg of active ingredient may be made as follows:

	Quantity (mg/suppository)
Active Ingredient	225
Saturated fatty acid glycerides	2000
Total	2225

The active ingredient is passed through a No 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.



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*Formulation 7*

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

Active Ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mL
Benzoic acid solution	0.10 mL
Flavour	q.v.
Color	q.v.
Purified water to total	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

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*Formulation 8*

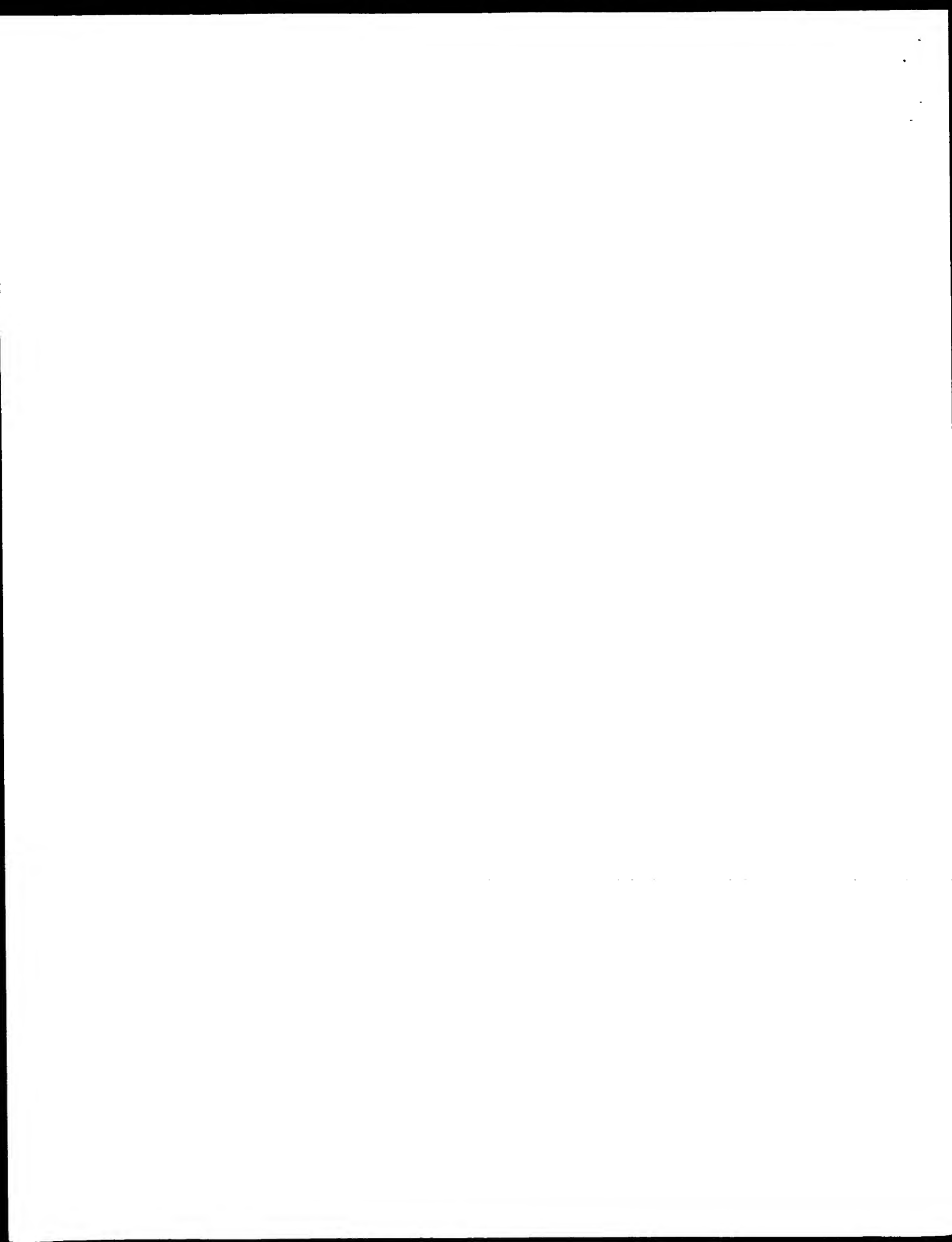
An intravenous formulation may be prepared as follows:

	Quantity
Active Ingredient	100 mg
Mannitol	100 mg
5 N Sodium hydroxide	200 mL
Purified water to total	5 mL

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*Formulation 9*

A topical formulation may be prepared as follows:



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	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White soft paraffin to	100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

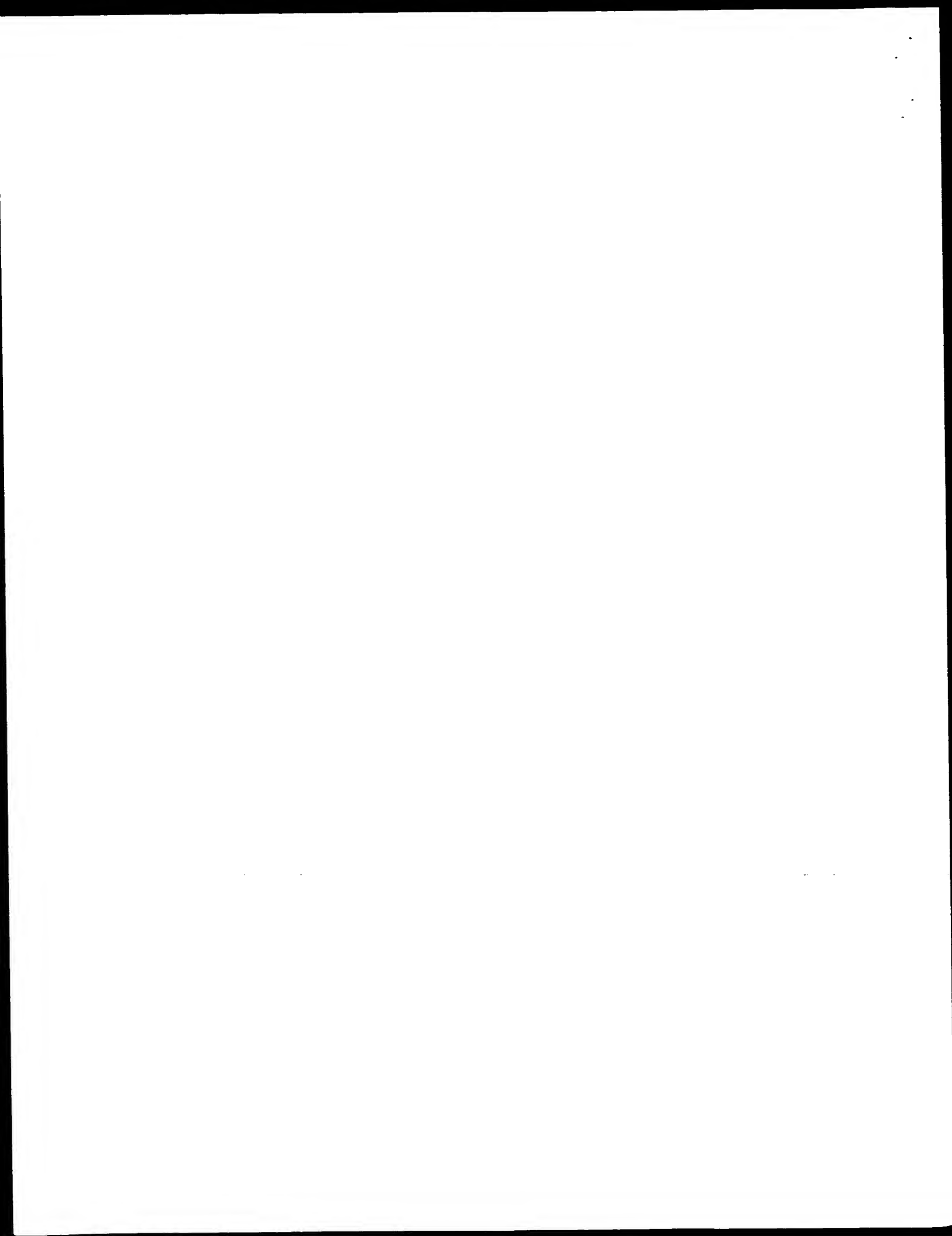
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#### *Formulation 10*

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

	Quantity (mg/tablet)
Active Ingredient	10.0
Glycerol	210.5
Water	143.0
Sodium Citrate	4.5
Polyvinyl Alcohol	26.5
Polyvinylpyrrolidone	15.5
Total	410.0

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90 °C. When the polymers have gone into solution, the solution is cooled to about 50°-55 °C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size





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Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts.

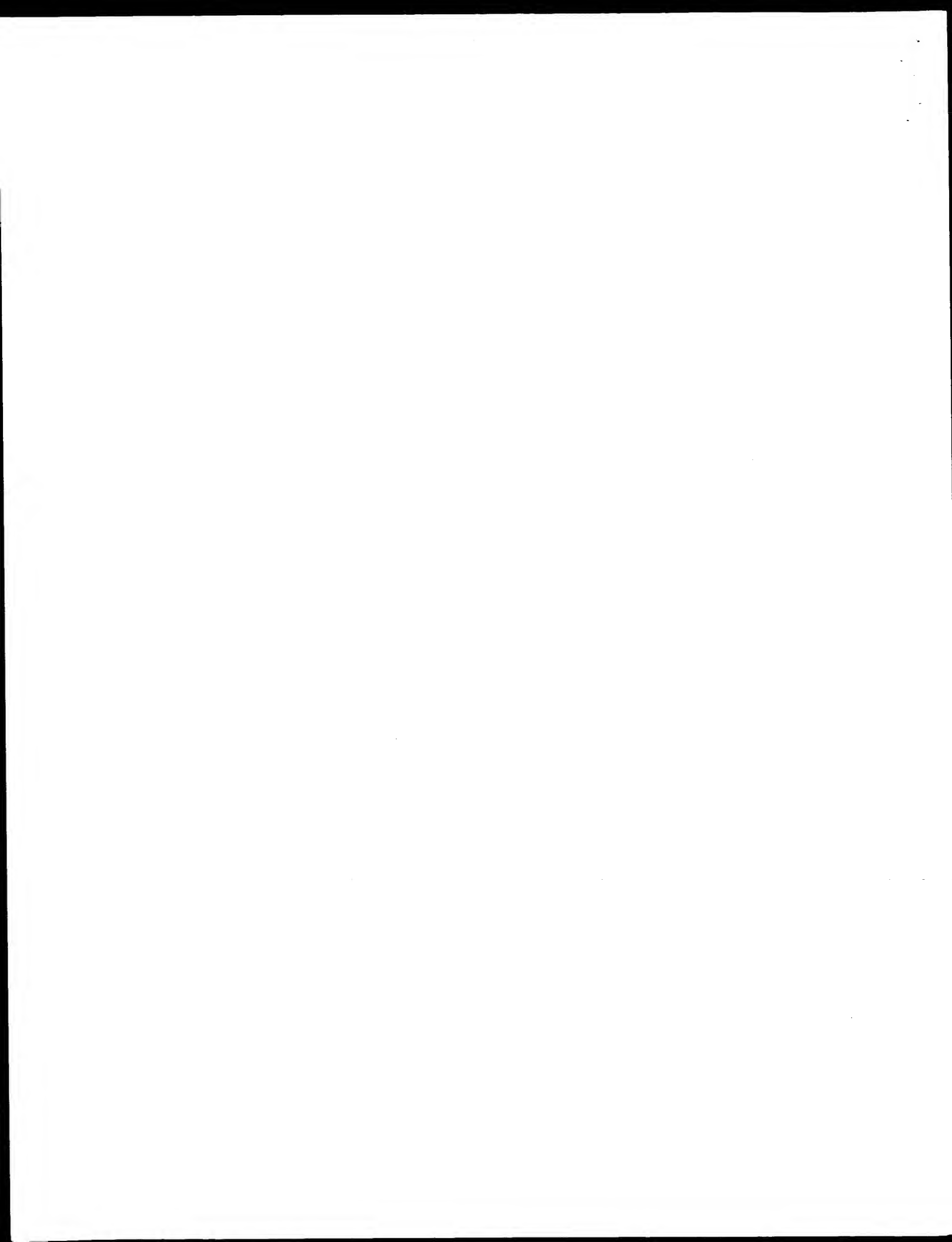
The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, for example, U.S. Pat. No. 5,023,252, issued Jun. 11, 1991) herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Pat. No. 5,011,472, issued Apr. 30, 1991, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions that can transiently open the blood-brain barrier.

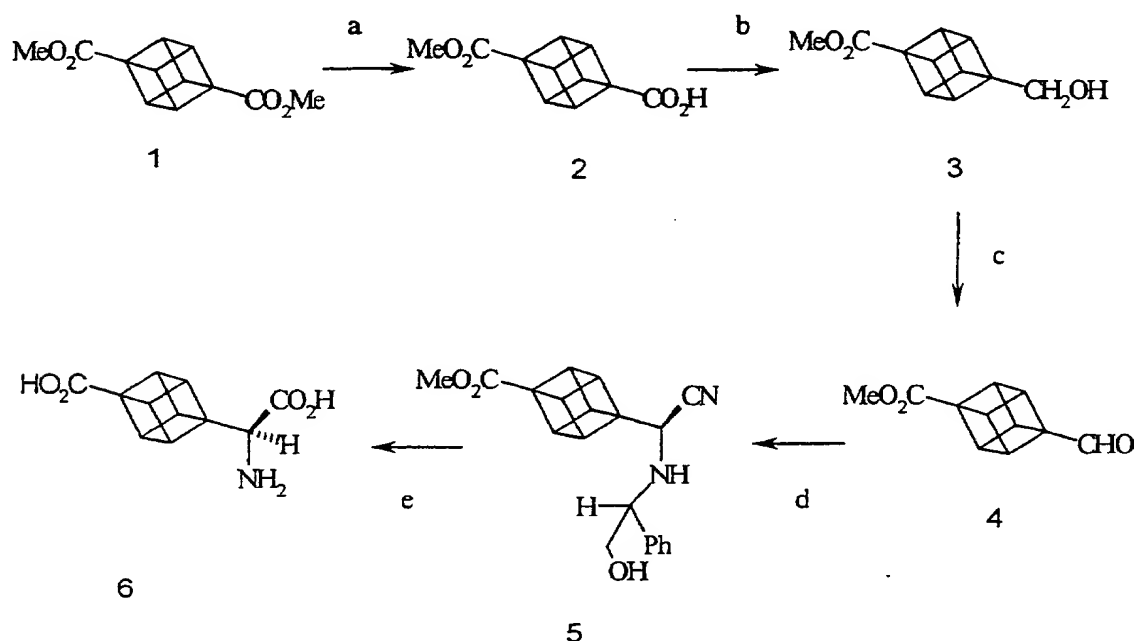
## EXAMPLES

The following Examples illustrate the invention. The following abbreviations are used in the Examples: EtOAc, ethyl acetate; THF, tetrahydrofuran; EtOH, ethanol; TLC, thin layer chromatography; GC, gas chromatography; HPLC, high pressure liquid chromatography; m-CPBA, m-chloroperbenzoic acid; Et<sub>2</sub>O, diethyl ether; DMSO, dimethyl sulfoxide; DBU, 1,8-diazabicyclo-[5.4.0]undec-7-ene; MTBE, methyl *t*-butyl ether; FDMS, field desorption mass spectrometry and *rt*, room temperature.



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## Example 1: Synthesis of Cubanylglycinates IGT 1.0 series

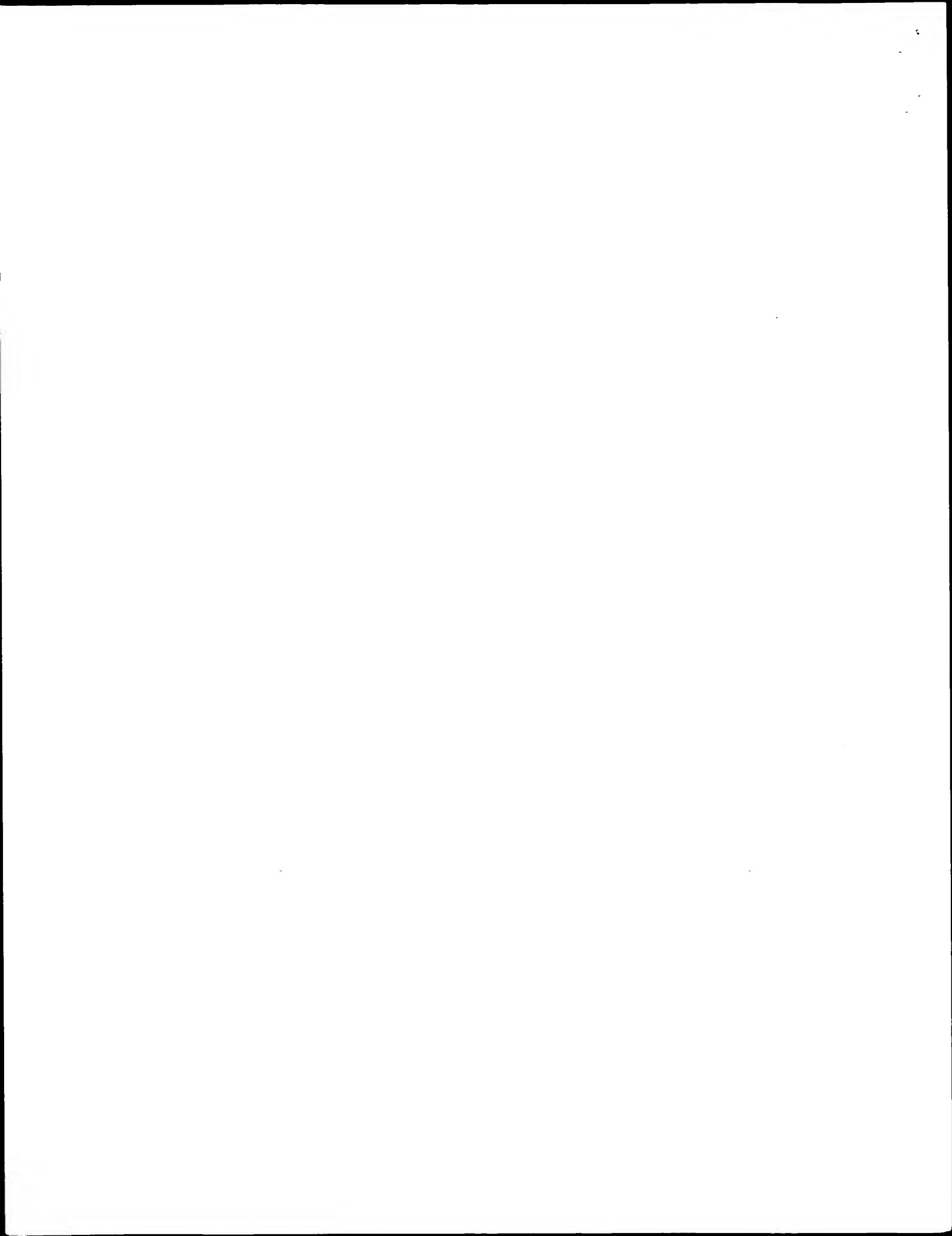
*Preparation 1: 4-methoxycarbonylcubane carboxylic acid*

A solution of cubane dimethyl ester (6.0g, 27.24 mmol) in 182 mL of dry THF is stirred under  $N_2$  at room temperature. A solution of methanolic NaOH (26.7 mmol, 10.7 mL 2.5 M) is added dropwise from a pressure equalized addition funnel and the resulting solution stirred at room temperature for 16 h. The mixture is evaporated under reduced pressure at r.t., the residue is taken up in 66 mL of water and extracted with 3 x 25 mL of chloroform. The aqueous layer is acidified to pH 3 with concentrated HCl and extracted with 3 x 30 mL of chloroform. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give (2) 182-183 °C:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.72 (s, 3H), 4.27 (m, 6H).

Yield 5.1 g (91%).

*Preparation 2: 4-methoxycarbonyl-1-(hydroxymethyl) cubane*

The mono acid (2) (0.48 g) is dissolved in dry THF (5 mL) and cooled to -70 °C. A solution of  $BH_3$  in THF is added slowly with stirring. The reaction mixture is stirred at -78 °C for 4 hrs and



allowed to come to room temperature. Water (3 mL) is added and stirred for 30 min, potassium carbonate (0.85 g) is added and the solution extracted with Et<sub>2</sub>O. The organic phase is dried over magnesium sulfate and evaporated to give the alcohol (3) 0.46 g (100%) m.p. 83-85 °C. <sup>1</sup>H NMR (200 MHz, solvent) δ: 1.58 (s, 1H), 3.62 (s, 3H), 3.72 (s, 2H), 3.81 (m, 3H), 4.1 (m, 3H).

*Preparation 3: 4-methoxycarbonyl-1-(formyl) cubane*

DMSO (0.7 mL, 9.68 mmol) is added to oxalyl chloride (0.42 mL, 4.84 mmol) in 12 mL of CH<sub>2</sub>Cl<sub>2</sub> at -78 °C. The alcohol (3) (0.46 g, 2.42 mmol) in 3 mL CH<sub>2</sub>Cl<sub>2</sub> is added and stirred at -78 °C for 1.5 h. Triethylamine (2.0 mL, 14.4 mmol) is added and the mixture is allowed to come to 0 °C. Saturated ammonium chloride solution is added and the phases separated, the aqueous layer is extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers are dried (MgSO<sub>4</sub>), then evaporated to give crude product which is purified by flash chromatography (1:1 hexanes:diethyl ether) to give 0.35 g (76%) of pure product (4). <sup>1</sup>H NMR (200 MHz, solvent) δ: 3.7 (s, 3H), 4.2 (m, 3H), 4.32 (m, 3H), 9.72 (s, 1H).

*Preparation 4: 4-methoxycarbonyl-1-[2'-hydroxy-1'-phenylethyl] methylnitrilocubane*

(R)-phenylglycinol (257 mg, 1.87 mmol) is added to a solution of the aldehyde (4) (0.35 g, 1.84 mmol) in 14 mL of methanol. The solution is cooled to 0 °C and TMSCN (0.49 mL, 3.68 mmol) is added and the mixture stirred at 0 °C overnight. Evaporation of the solvent leaves a residue which is purified by chromatography (diethyl ether:hexanes, 3:1) to give 0.48 g (77%) of pure product (5). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 2.23 (s, 1H), 2.6 (br, 1H), 3.5-3.75 (m, 2H), 3.7 (s, 3H), 3.9 (m, 3H), 4.11 (dd, 1H), 4.2 (m, 3H), 7.3 (s, 5H).

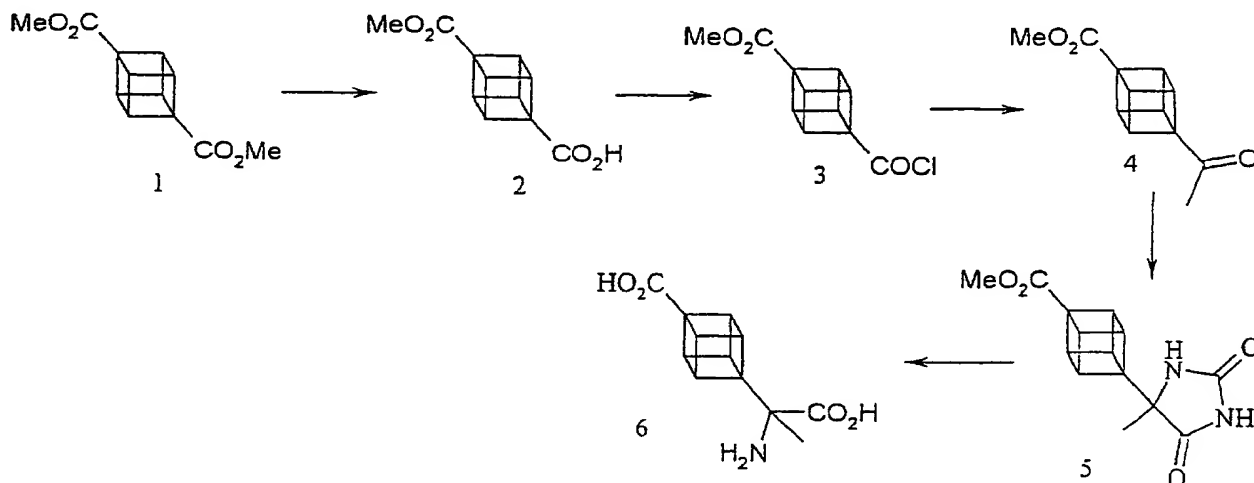
*Preparation 5: 4-carboxy-1-cubanylglycine*

Lead acetate (0.69 g, 1.57 mmol) is added to a stirred solution of nitrile (5) (0.48 g, 1.42 mmol) in dry methanol/dichloromethane 1:1 (12 mL). After 10 min 10 mL of water is added and the suspension filtered through celite. The organic layer is dried and evaporated to give the crude imine. The crude imine is refluxed with 6N HCl (30 mL) for 6 hr. The solution is evaporated to dryness and placed on anion exchange resin, eluting with 1N acetic acid to yield the product (6). mp. 241 °C (dec.) <sup>1</sup>H NMR (D<sub>2</sub>O) δ 3.96 (s, 1H), 4.01 (m, 3H), 4.14 (m, 3H).



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## Example 2

*Preparation 1: 4-methoxycarbonylcubane carboxylic acid*

A solution of cubane dimethyl ester (6.0g, 27.24 mmol) in 182 mL of dry THF is stirred under  $N_2$  at r.t. a solution of methanolic NaOH (26.7 mmol, 10.7 mL 2.5 M) is added dropwise from a pressure equalized addition funnel and the resulting solution stirred at r.t. for 16 h. The mixture is evaporated under reduced pressure at r.t., the residue is taken up in 66 mL of water and extracted with 3 x 25 mL of chloroform. The aqueous layer is acidified to pH 3 with concentrated HCl and extracted with 3 x 30 mL of chloroform. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give (2) 182-183 °C:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.72 (s, 3H), 4.27 (m, 6H). Yield 5.1 g (91%).

*Preparation 2: 4-methoxycarbonylcubane-1-carbonyl chloride*

The monomethyl ester (2) (1.37 g, 6.65 mmol) is dissolved in 15 mL of thionyl chloride and gently refluxed overnight. The thionyl chloride is evaporated off and the resultant residue containing (3) was used immediately without further purification.





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*Preparation 3: 4-methoxycarbonylcubane-1-methyl ketone*

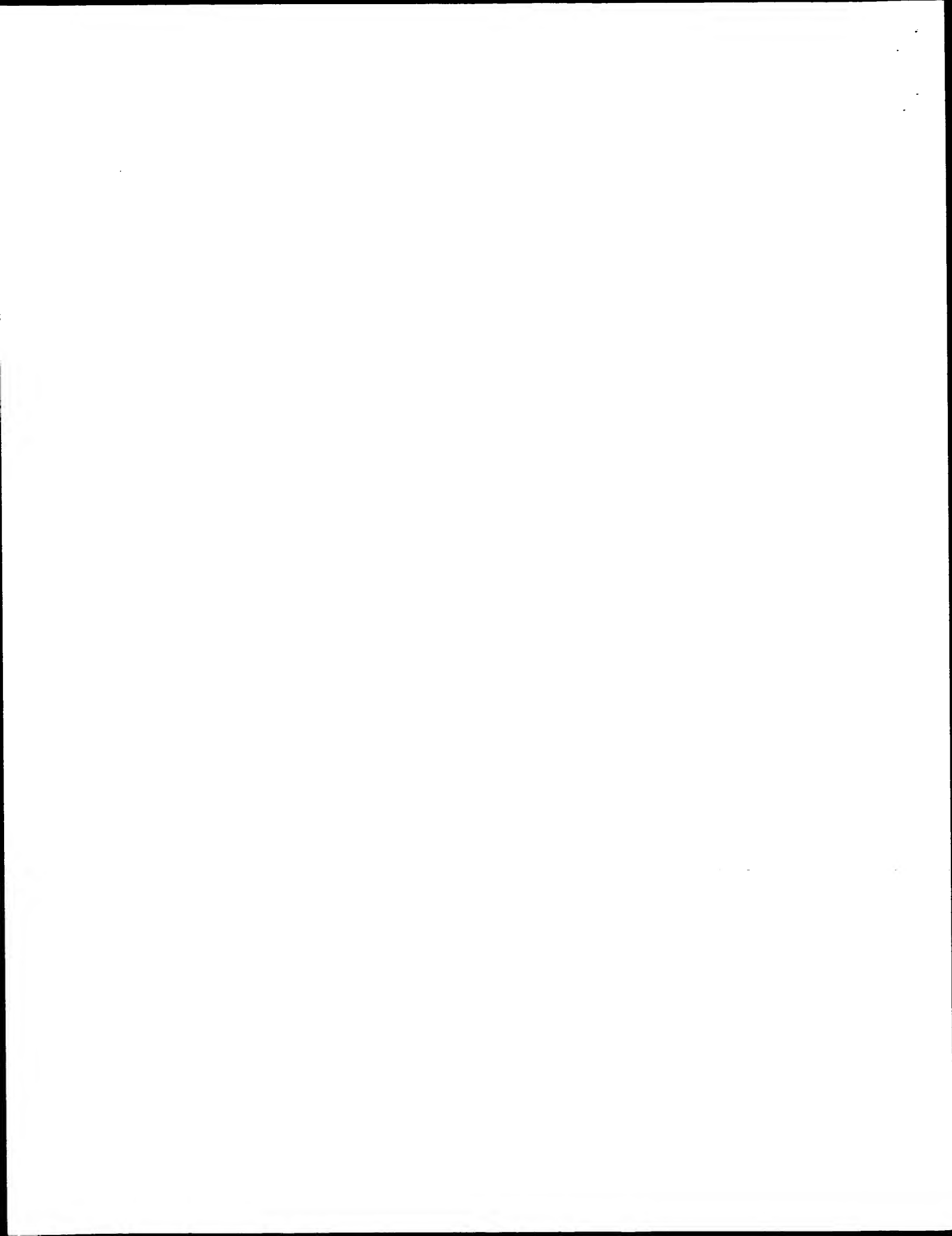
A suspension of copper iodide (1.49 g, 7.83 mmol) in 30 mL of dry THF is stirred at 0°C. Methyl lithium (15.75 mmol, 11.2 mL of 1.4 M) was added and stirred at 0°C for 30 min, then cooled to -78°C. A solution of 1.6 g, 7.12 mmol of (3) in 10 mL dry THF is added and the resultant mixture stirred for 1 h. at -78°C. The mixture was quenched with saturated ammonium chloride solution (15 mL) and extracted with 3 x 30 mL of diethyl ether. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give crude (4). The product was purified by silica chromatography (hexanes:ethyl acetate, 2:1) to give 1.0 g of product (yield 69%). m.p. 87-89°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.17 (s, 3H), 3.7 (s, 3H), 4.21 (m, 6H).

*Preparation 4: 4-methoxycarbonylcubane-1-methyl-1-(5,5'-hydantoin)*

A solution of the methyl ketone (4) (1.0 g, 4.9 mmol) in 40 mL of ethanol and 5.8 mL of 1 N NaOH, is stirred at 70°C for 4 h. The resulting solution is evaporated to dryness under reduced pressure and redissolved in 1:1 ethanol: water (20 mL). To this solution is added potassium cyanide (0.35 g, 5.4 mmol) and ammonium carbonate (0.96 g, 9.8 mmol) and the mixture heated in a sealed tube at 85°C for 24 h. The reaction is cooled, acidified with 6 N HCl and reduced in volume until a precipitate forms. The precipitate is filtered and the filtrate evaporated to dryness and extracted with ethyl acetate. The solvent is evaporated and the product combined with the residue from above to give (5) as a white solid. Yield 0.95 g (75%) m.p. 244-248°C. NMR  $^1\text{H}$  (DMSO)  $\delta$  1.18 (s, 3H) 3.9 (m, 3H), 4.0 (m, 3H), 8.1 (s, 1H), 10.6 (s, 1H).

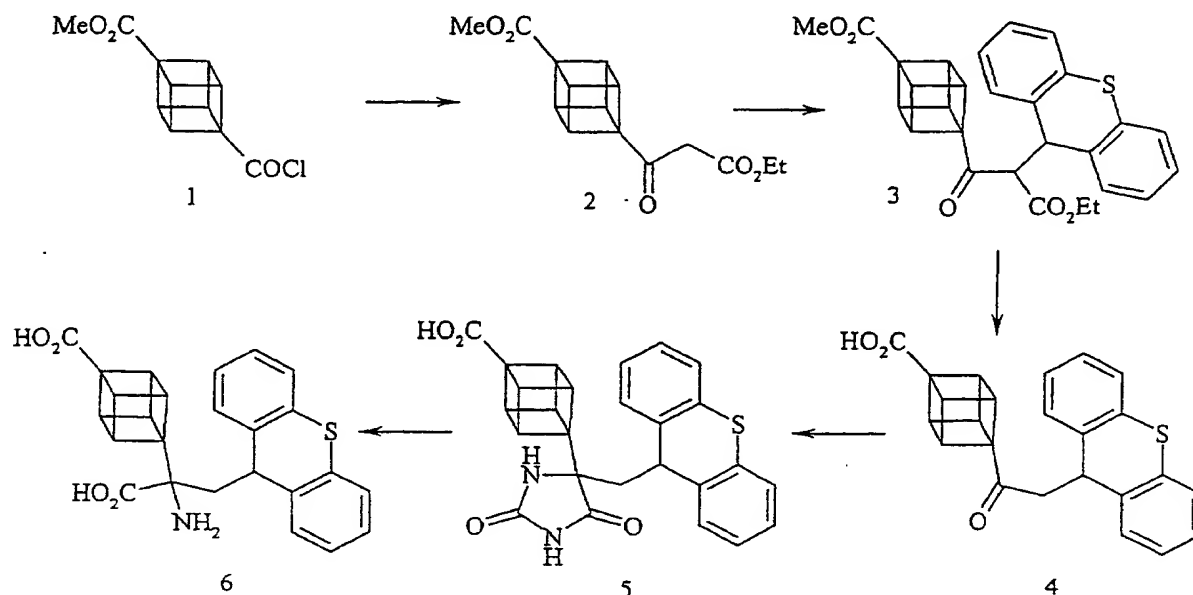
*Preparation 5: 4-carboxycubane-1-methylglycine*

The hydantoin (5) (0.95 g, 3.65 mmol) is dissolved in 30 mL of 2 N NaOH and heated to 170°C in a sealed tube for 20 h. The reaction is cooled and filtered to remove precipitate and the filter cake washed with 3 x 10 mL of water. The combined aqueous washings are evaporated to give crude (6) which is applied to Spectrum 1X4 anion exchange resin, eluted with 0.5 N acetic acid. Isolation by evaporation and crystallization gives (6) as colorless crystals. m.p. >250°C (decomp.) NMR.  $^1\text{H}$  ( $\text{D}_2\text{O}$ )  $\delta$  1.38 (s, 3H), 3.95 (s, 6H)

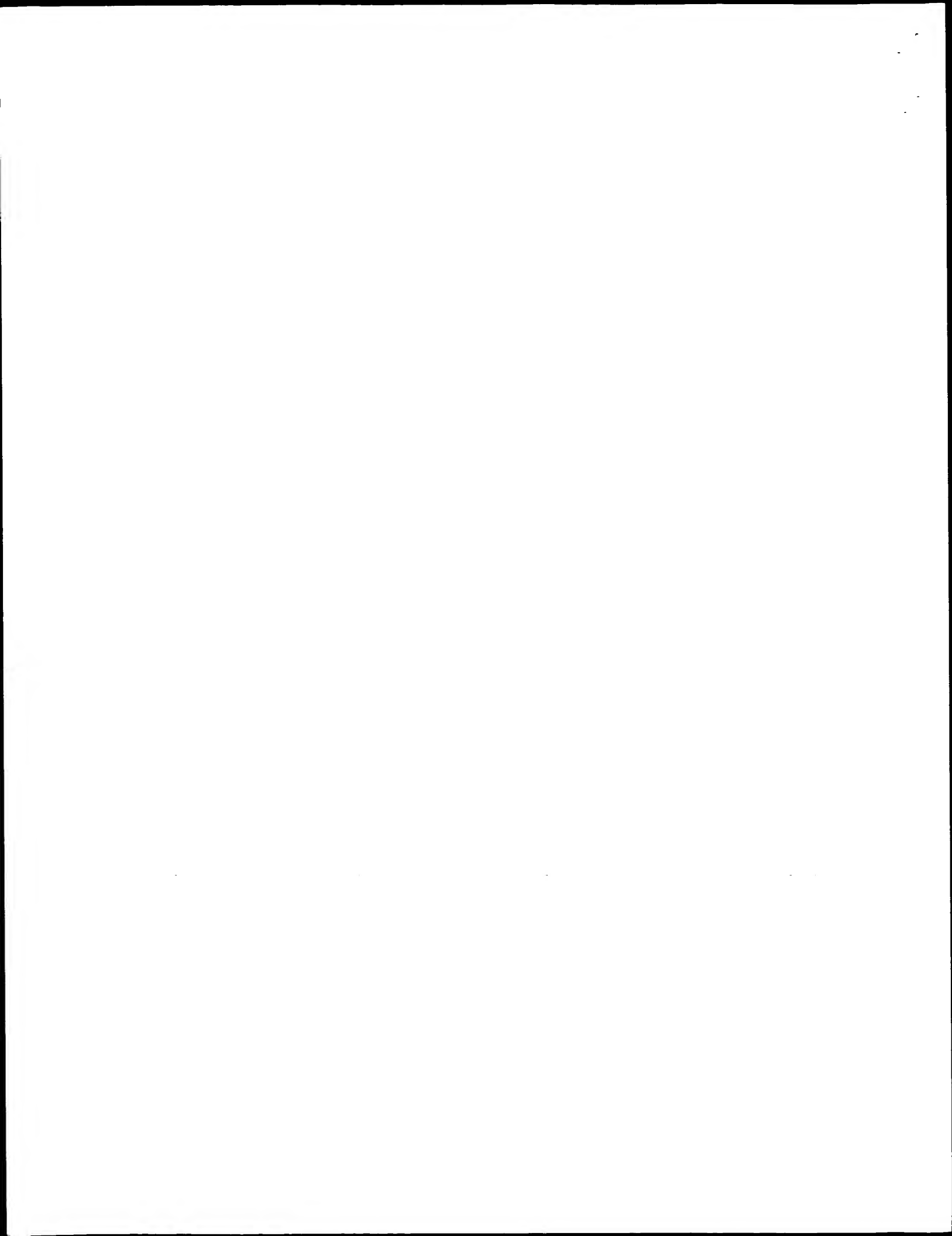


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## Example 3

*Preparation 1: 4-methoxycarbonylcubane-1-acyl ethylcarboxylate.*

n-butyl lithium (34.83 mmol, 23.5 mL of 1.5 M) is added dropwise to a stirred solution of ethyl hydrogen malonate (2.32 g, 17.41 mmol) in 80 mL of dry THF under  $\text{N}_2$  at  $-78^\circ\text{C}$ . The mixture was warmed to  $-30^\circ\text{C}$  over 0.5 h and then re-cooled to  $-78^\circ\text{C}$ . The acid chloride of cubane monomethyl ester from example (2) above (2.35 g, 10.46 mmol) in 7 mL of THF is added dropwise to the stirred solution. The reaction is warmed slowly to r.t and stirred for a further 1 h. The solution is poured into 50 mL of 1 N HCl and extracted with 3 x 50 mL of diethyl ether. The combined organic extracts are further extracted with 20 mL of saturated sodium hydrogen carbonate and brine, dried over magnesium sulphate, filtered and evaporated to give crude (2). The product is purified by column chromatography on silica with hexanes: ethyl acetate 2:1 to yield 2.5 g (86%) of (2).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.2 (t, 3H) 3.4 (s, 2H), 3.65 (s, 3H), 4.2 (m, 8H).



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*Preparation 2:* 4-methoxycarbonylcubane-1-(thioxanthyl)-acetyl ethylcarboxylate.

cubane- $\beta$ -ketoester (2) (1.15g, 4.16 mmol) and thioxanthene-9-ol (0.88g, 4.1 mmol) are dissolved in 18 mL of a 1:1 mixture of ethanol:acetic acid and stirred at r.t. for 3 days. The resulting crystalline solid was filtered off to yield 1.52 g (77%) of pure (3) m.p. 147-149°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.00 (t, 3H), 3.24 (s, 3H), 3.75 (m, 3H), 3.9 (q, 2H), 4.0 (m, 3H), 4.6 (d, 1H), 5.0 (d, 1H), 7.3 (m, 8H).

*Preparation 3:* 4-carboxycubane-1-methylthioxanthylketone

The thioxanthylcubane adduct (3) (1.69 g, 3.57 mmol) is dissolved in ethanol 33 mL and 8.7 mL of 1 N NaOH and heated at 70°C for 4 h. The resulting solution is evaporated and redissolved in 25 mL of water, acidified with 6 N HCl and extracted with 3 x 50 mL of diethyl ether. The combined organic layers are dried over magnesium sulphate, filtered and concentrated to give a crude product containing (4). Chromatography on silica using ethyl acetate gives 1.26 g (88%) of (4)

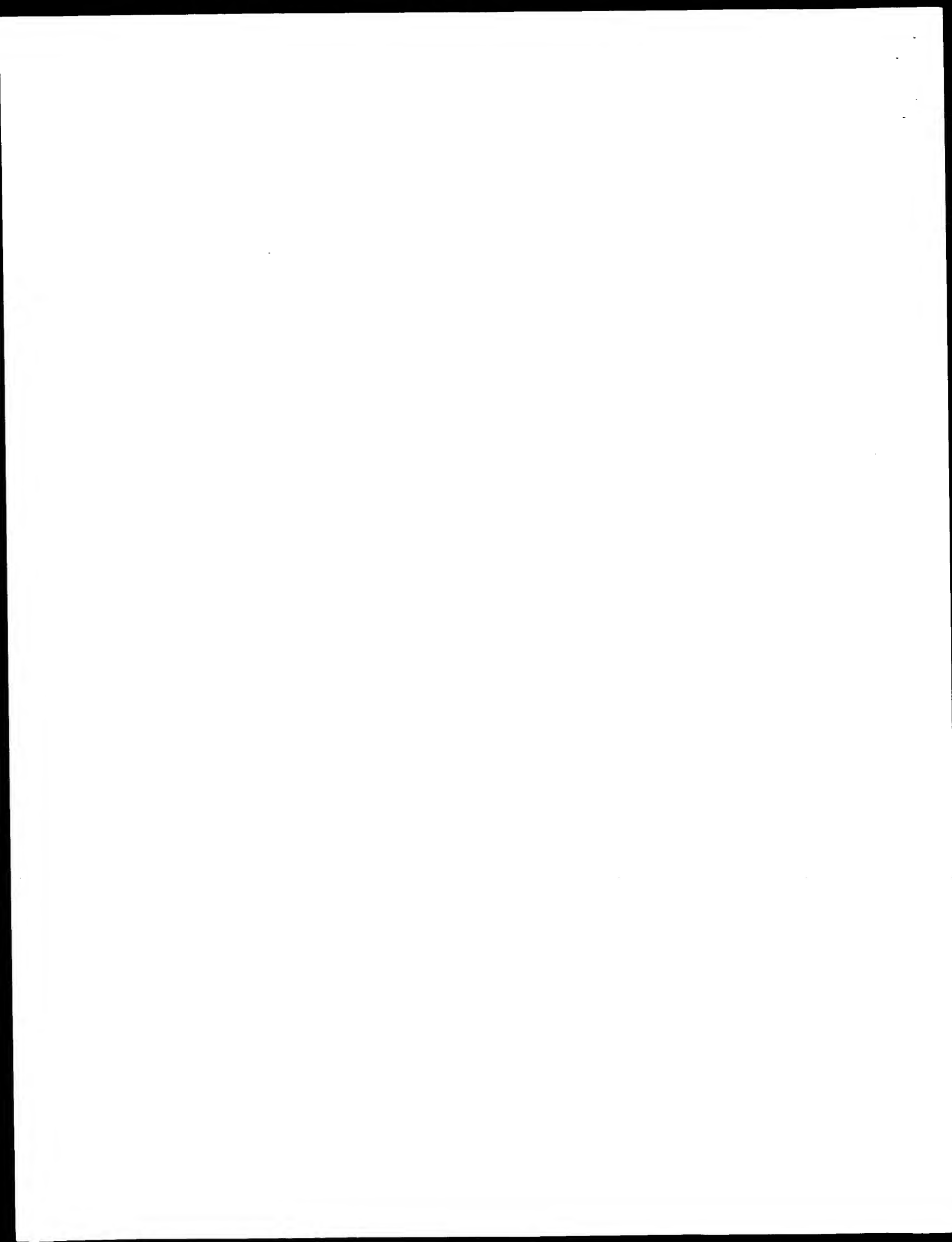
$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.8 (d, 2H), 3.8 (m, 3H), 4.0 (m, 3H), 4.7 (t, 1H), 7.3 (m, 8H), 9.5 (br, 1H).

*Preparation 4:* 4-carboxycubane-1-thioxanthyl-1-(5,5'-hydantoin)

The thioxanthyl cubane ketone (4) (1.24 g, 3.22 mmol) is dissolved in 1 l ethanol:water (20 mL). Potassium cyanide (0.522 g, 8.0 mmol) and ammonium carbonate (1.39 g, 14.4 mmol) are added and the solution heated in a sealed tube at 85°C for 65 h. The reaction is cooled and acidified with 2 N HCl and extracted with 3 x 40 mL of ethyl acetate. The organic layers are combined, dried over magnesium sulphate, filtered and evaporated to give (5) 1.3 g (88%) as a crude product. This material was hydrolyzed in the next step without purification.

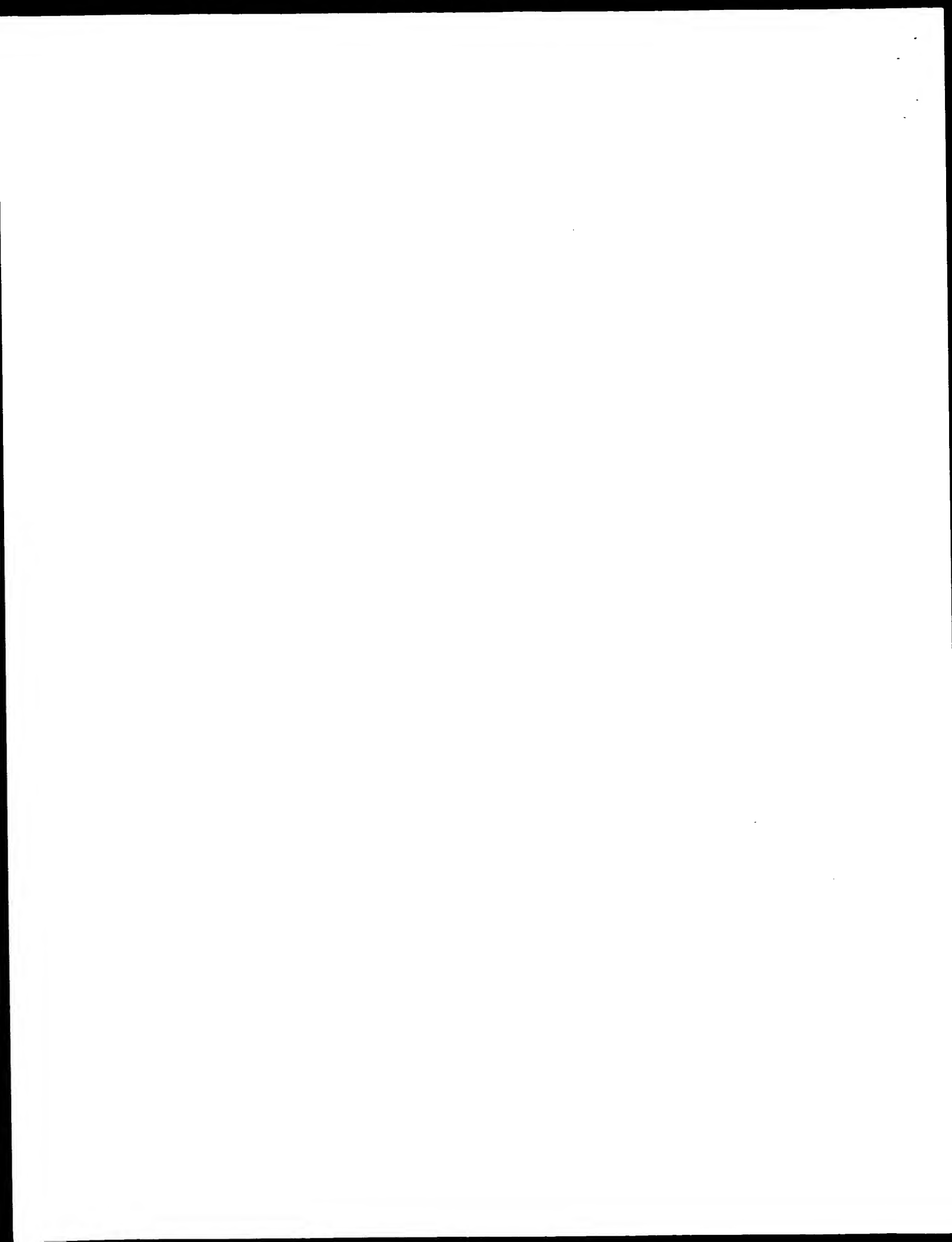
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  1.7 (m, 1H), 2.7 (m, 1H), 3.8 (m, 3H), 4.0 (m, 3H), 4.3 (m, 1H), 7.4 (m, 8H).

*Preparation 5:* 4-carboxycubane-1- thioxanthyl lglycine



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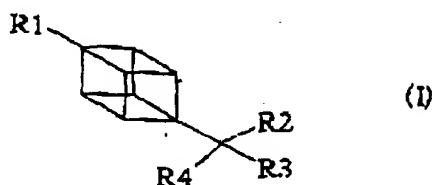
The hydantoin adduct (5) (300 mg, 0.65 mmol) is taken up in 1 N NaOH (10 mL) and heated at 170 °C for 20 h in a sealed tube. The mixture is cooled and the pH adjusted with 6 N HCl to between 7 and 8. The precipitate formed is filtered and washed with water. The combined filtrate and washings are combined and evaporated to dryness. The resulting residue is purified by column chromatography and finally by reverse phase chromatography to yield (6) as colorless crystals. 70 mg. <sup>1</sup>H NMR (CD<sub>3</sub>OD + D<sub>2</sub>O) δ 2.3 (m, 2H), 3.9 (s, 6H), 4.4 (m, 1H), 7.4 (m, 8H)





**We claim:**

1. A compound of the formula:



wherein:

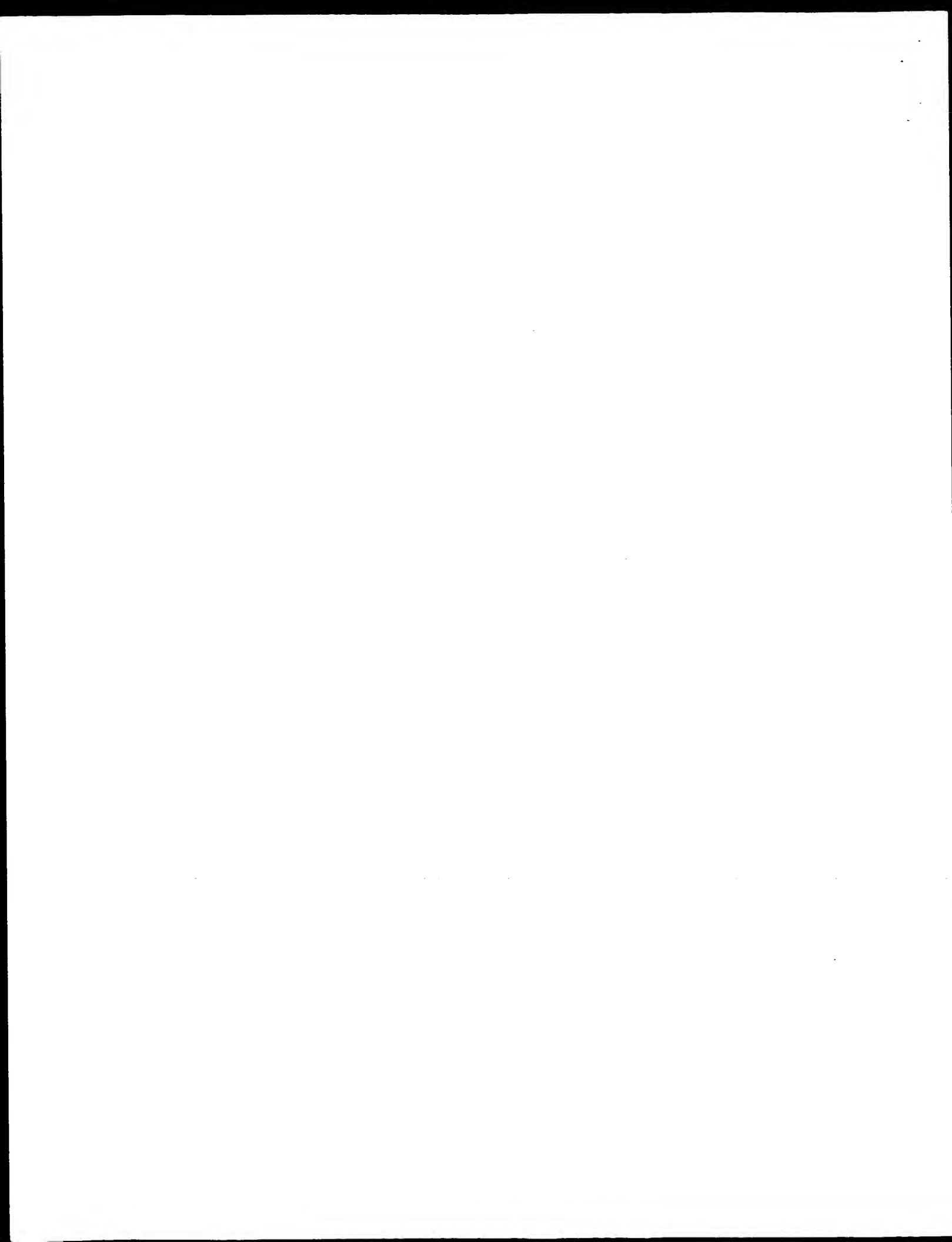
**R1** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfono, -CH<sub>2</sub>-sulfinio, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, and -CH<sub>2</sub>-isoxazol;

**R2** can be a basic group selected from the group consisting of 1° amino, 2° amino, 3° amino, quaternary ammonium salts, aliphatic 1° amino, aliphatic 2° amino, aliphatic 3° amino, aliphatic quaternary ammonium salts, aromatic 1° amino, aromatic 2° amino, aromatic 3° amino, aromatic quaternary ammonium salts, imidazol, guanidino, boronoamino, allyl, urea, thiourca,

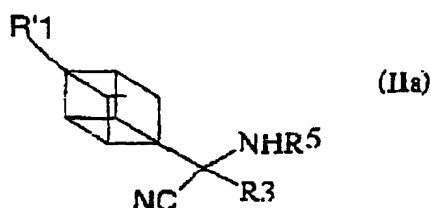
**R3** can be H, aliphatic, aromatic or heterocyclic;

**R4** can be an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfono, sulfinio, borono, tetrazol, isoxazol; and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, wherein **R1** is COOH.
3. A compound as claimed in claim 1, wherein **R2** is NH<sub>2</sub>.
4. A compound as claimed in claim 1, wherein **R3** can be -H, or -Me, or xanthyl or thioxanthyl or -CH<sub>2</sub>-xanthyl, or -CH<sub>2</sub>-thioxanthyl and **R4** is -COOH.

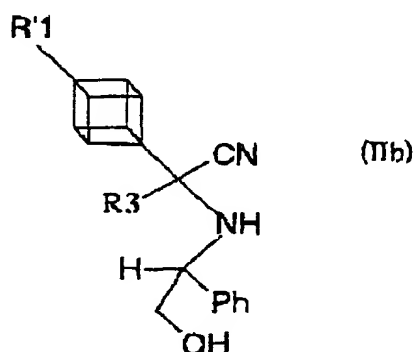


5. A process for the preparation of a compound of Formula I, or a pharmaceutically acceptable metabolically-labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, which comprises:
- (a) hydrolyzing a compound of formula:

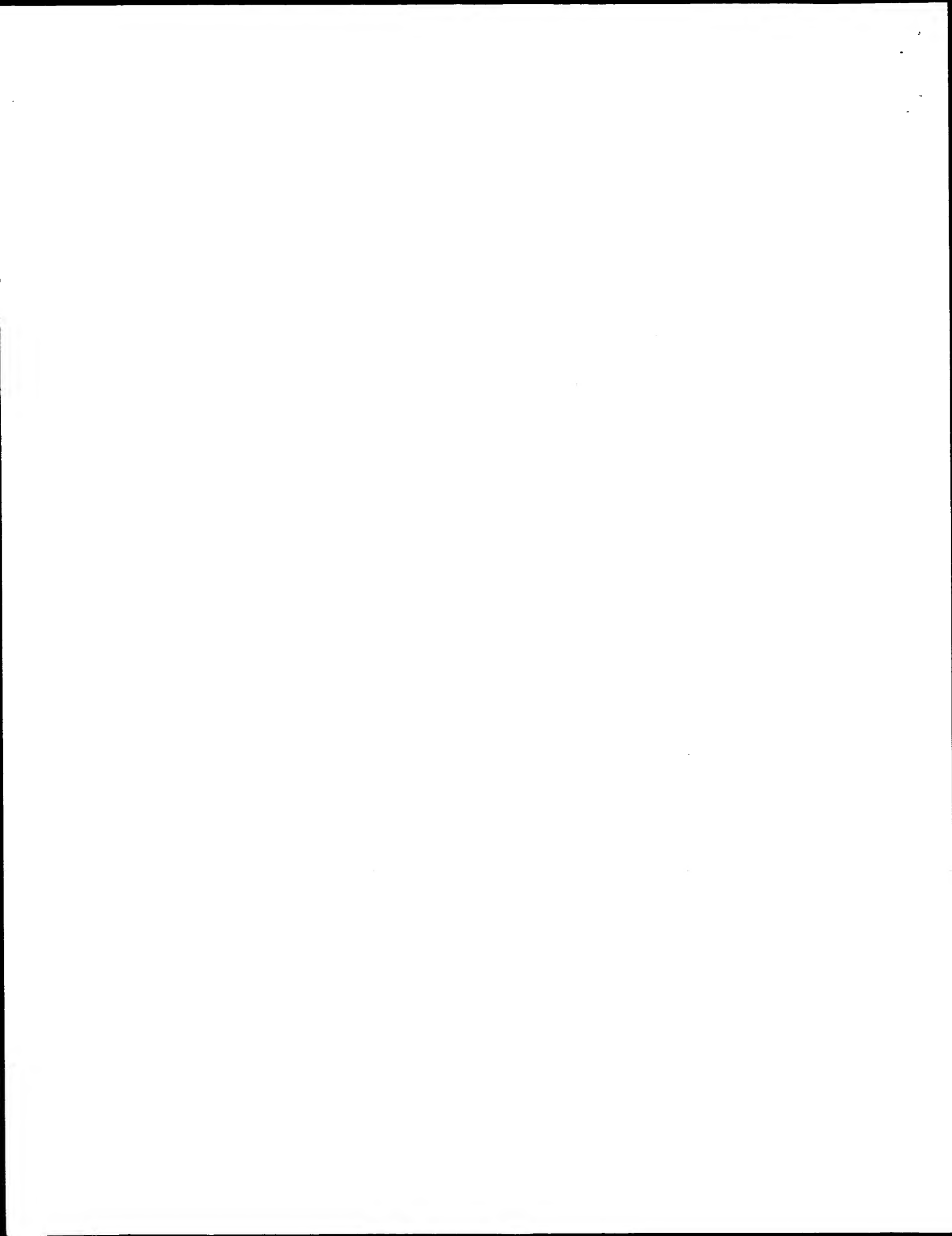


wherein: **R'1** is an acidic group selected from the group consisting of carboxyl, phosphono, phosphino, sulfonyl, sulfinyl, borono, tetrazol, isoxazol, -CH<sub>2</sub>-carboxyl, -CH<sub>2</sub>-phosphono, -CH<sub>2</sub>-phosphino, -CH<sub>2</sub>-sulfonyl, -CH<sub>2</sub>-sulfinyl, -CH<sub>2</sub>-borono, -CH<sub>2</sub>-tetrazol, -CH<sub>2</sub>-isoxazol and higher analogues thereof, or a protected form thereof, **R3** can be H, aliphatic, aromatic or heterocyclic and **R5** represents a hydrogen atom or an acyl group, and wherein preferred values for **R5** are hydrogen and (2-6C) alkanoyl groups, such as acetyl; or

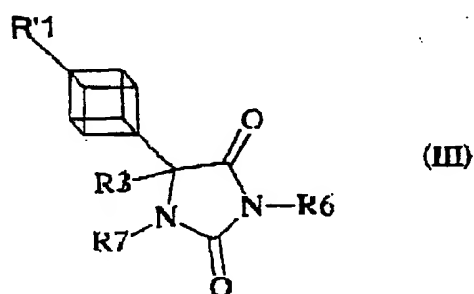
- (b) deprotecting and hydrolyzing a compound of formula (II b)



wherein: **R'1** and **R3** are as defined above; or

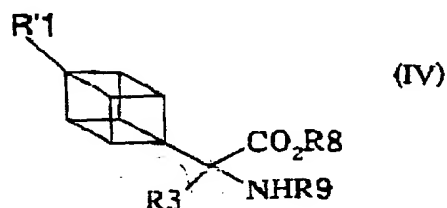


(c) hydrolyzing a compound of formula:



wherein: **R6** and **R7** each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof. **R'1** and **R3** are as defined above; or

(d) deprotecting a compound of formula:



wherein: **R8** represents a hydrogen atom or a carboxyl protecting group, or a salt thereof, and **R9** represents a hydrogen atom or a nitrogen protecting group, **R'1** and **R3** are as defined above;

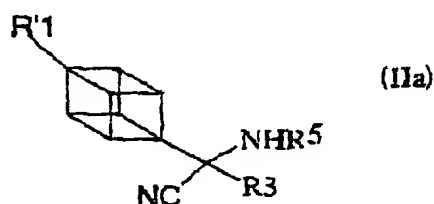
whereafter, if necessary and/or desired:

- (i) resolving the compound of Formula I;
- (ii) converting the compound of Formula I into a non-toxic metabolically-labile ester or amide thereof; and/or
- (iii) converting the compound of Formula I or a non-toxic metabolically-labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

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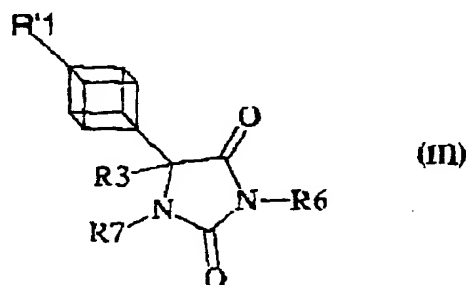


6. A pharmaceutical formulation, which comprises a compound as claimed in claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.
7. A use of the compound according to claim 1 to modulate one or more metabotropic glutamate receptor functions in a warm blooded mammal, wherein said use comprises administering an effective amount of a compound of formula (I) as claimed in claim 1.
8. A compound of formula:



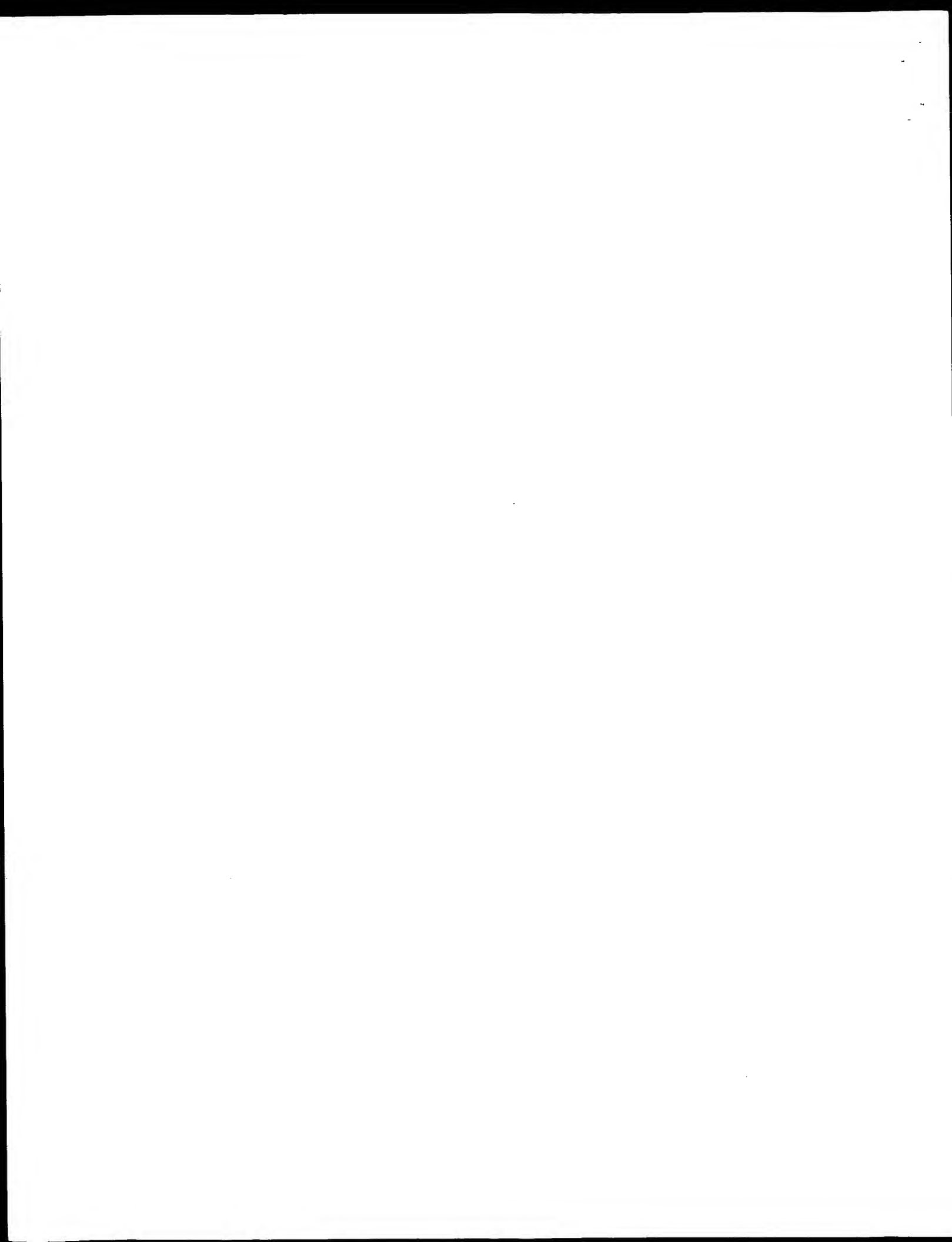
wherein: **R'1**, **R3** and **R5** have the meanings as defined in claim 5.

9. A compound of formula:



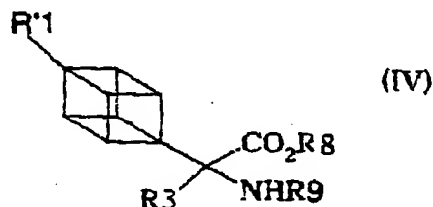
wherein: **R'1**, **R3**, **R6** and **R7** have meanings as defined in claim 5.

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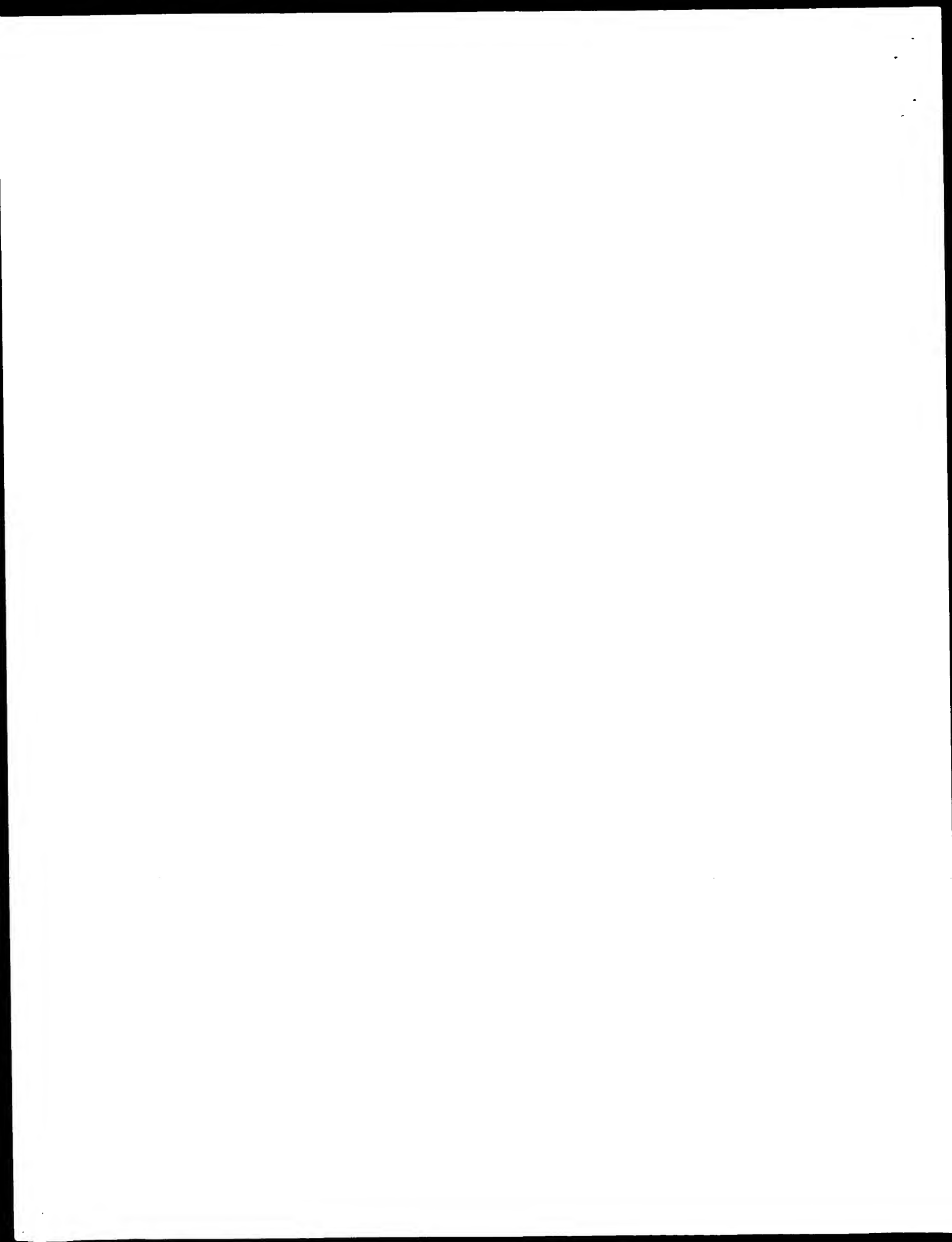
10. A compound of formula:



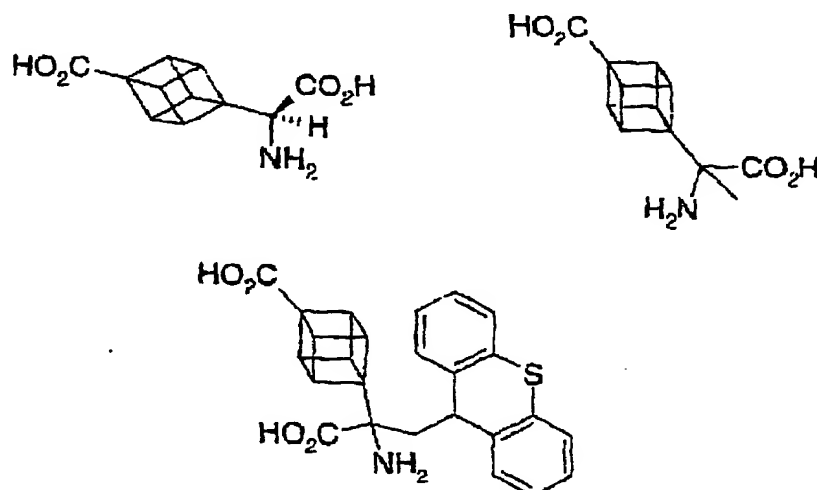
wherein: **R'1**, **R3**, **R8** and **R9** have meanings as defined in claim 5.

11. A compound according to claim 1, wherein **R1** is  $-\text{COOH}$ , **R2** is  $-\text{NH}_2$ , **R3** is  $\text{H}$  and **R4** is  $\text{COOH}$ .
12. A compound according to claim 1, wherein **R1** is  $-\text{COOH}$ , **R2** is  $-\text{NH}_2$ , **R3** is  $\text{CH}_3$  and **R4** is  $\text{COOH}$ .
13. A compound according to claim 1, wherein **R1** is  $-\text{COOH}$ , **R2** is  $-\text{NH}_2$ , **R3** is  $-\text{CH}_2$ -thioxanthyl and **R4** is  $\text{COOH}$ .
14. A use of the compound according to claim 1 for the treatment of a neurological disease or disorder selected from the group comprising: cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia, stroke, cardiac arrest, spinal cord trauma, head trauma, perinatal hypoxia, and hypoglycemic neuronal damage, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms, convulsions, migraine headaches, urinary incontinence, psychosis, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, anxiety and related disorders (e.g. panic attack), emesis, brain edema, chronic pain, sleep disorders, Tourette's syndrome, attention deficit disorder, and tardive dyskinesia, wherein said use comprises administering an effective amount of a compound of formula (I).

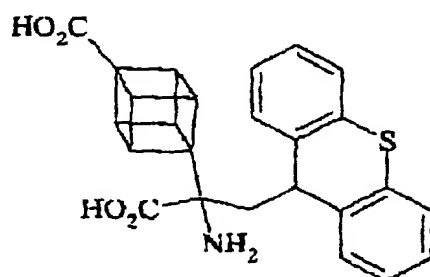
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15. A use of the compound according to claim 1 for the treatment of a psychiatric disease or disorder selected from the group comprising: schizophrenia, anxiety and related disorders (e.g. panic attack), depression, bipolar disorders, psychosis, and obsessive compulsive disorders, wherein said use comprises administering an effective amount of a compound of formula (I).
16. The use according to any one of claims 7, 14 or 15 wherein said compound is selected from the group of compounds comprising:

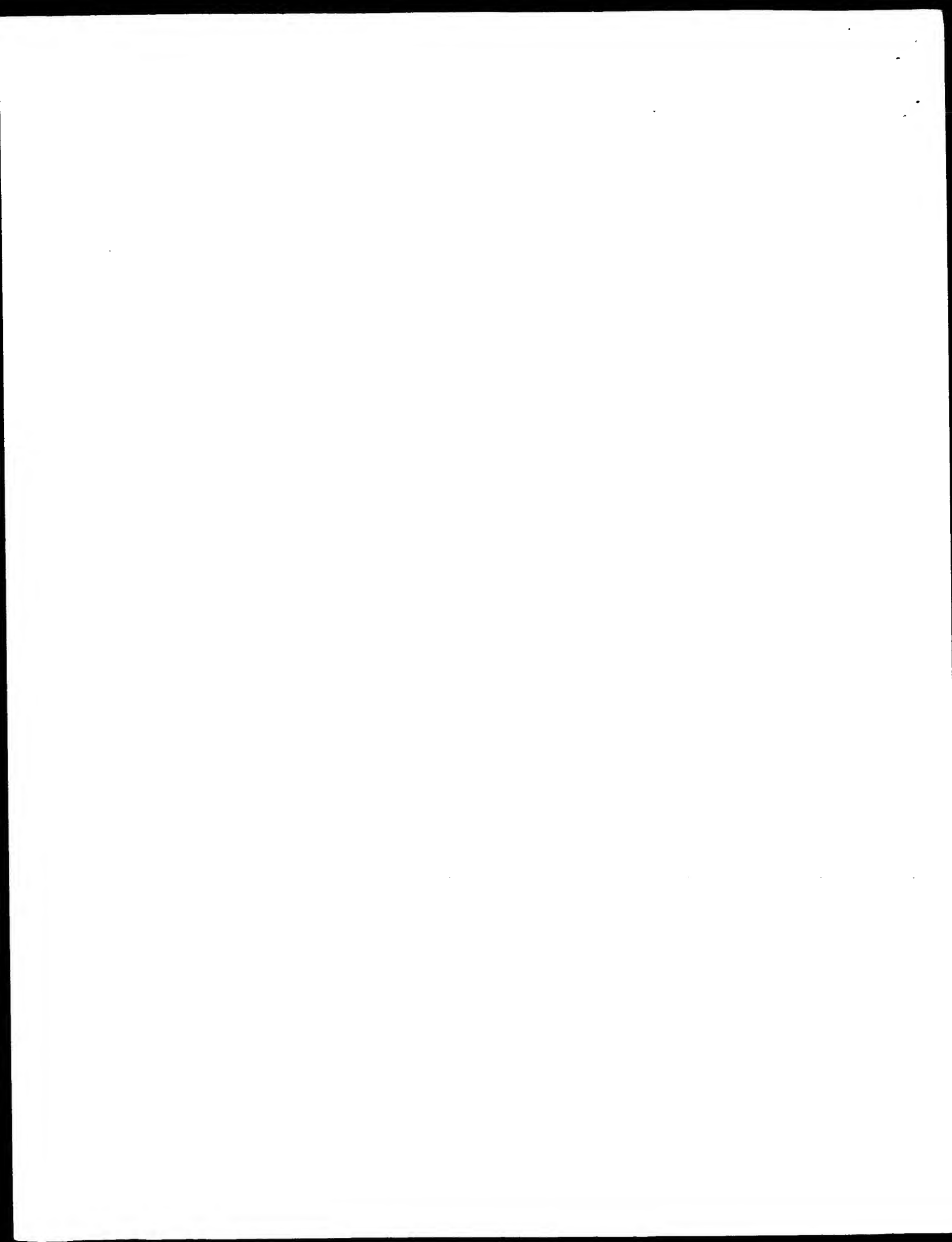


17. A use of the compound:

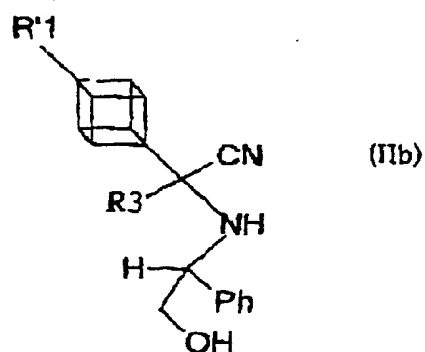


for the treatment of cerebral ischemia, stroke and cardiac arrest, wherein said use comprises administering an effective amount of the said compound.

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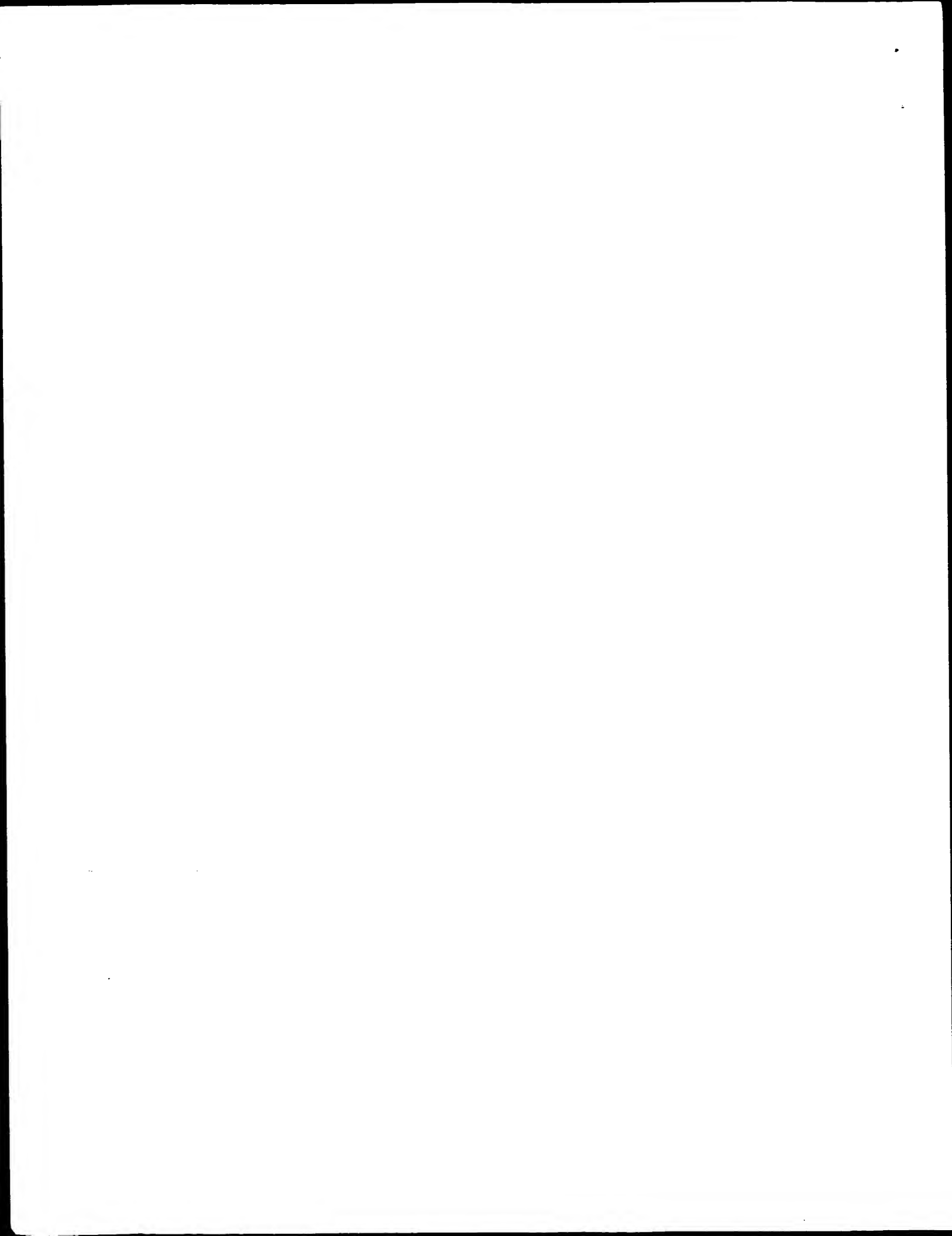
18. A compound of formula:



wherein: **R'1** and **R3** have the meaning as defined in claim 5.

19. A compound according to claim 18, wherein: **R'1** is -COOMe, **R3** is H.
20. A compound according to claim 9, wherein: **R'1** is -COOH, **R3** is CH<sub>3</sub>, **R6** = **R7** is H.
21. A compound according to claim 9, wherein: **R'1** is -COOH, **R3** is -CH<sub>2</sub>-thioxanthyl, **R6** = **R7** is H.

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PC

# REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only	
PCT / CA 9 / 00 311	
International Application No.	
19	APRIL 1999 (19.04.99)
International Filing Date	
RO/CA	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired) (12 characters maximum) 379-110PCT	

<b>Box No. I TITLE OF INVENTION</b>	
CUBANE ANALOGS WITH ACTIVITY AT THE METABOTROPIC GLUTAMATE RECEPTORS	
<b>Box No. II APPLICANT</b>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
CURRY, Kenneth 1176 East King Edward Avenue Vancouver, British Columbia V5V 2G2 Canada	<input checked="" type="checkbox"/> This person is also inventor. Telephone No. Facsimile No. Teleprinter No.
State (that is, country) of nationality: CA	State (that is, country) of residence: CA
This person is applicant for the purposes of: <input checked="" type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
<b>Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)</b>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
PAJOUHESH, Hassan Suite 601, 1020 Harwood Street Vancouver, British Columbia V6E 1S1 Canada	This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality: IRAN	State (that is, country) of residence: CA
This person is applicant for the purposes of: <input checked="" type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
<input type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.	
<b>Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE</b>	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
MBM & Co. P.O. Box 809, Station B Ottawa, Ontario K1P 5P9 Canada	Telephone No. (613) 567-0762 Facsimile No. (613) 563-7671 Teleprinter No.
<input type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	



**No.V DESIGNATION OF STATES**

The following designations are made under Rule 4.9(a) (mark the applicable boxes; at least one must be marked):

**Regional Patent**

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

**National Patent (if other kind of protection or treatment desired, specify on dotted line):**

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> AL Albania                               | <input checked="" type="checkbox"/> LS Lesotho                                   |
| <input checked="" type="checkbox"/> AM Armenia                               | <input checked="" type="checkbox"/> LT Lithuania                                 |
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| <input checked="" type="checkbox"/> LC Saint Lucia                           |  |
| <input checked="" type="checkbox"/> LK Sri Lanka                             |  |
| <input checked="" type="checkbox"/> LR Liberia                               |  |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ All member states *A.F. United Arab Emirates*
- ☐ *2 A. S.W.T.H. A.F.R.I.C.A.*

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)



<b>No. VI PRIORITY CLAIM</b>					<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:			
		national application: country	regional application: regional Office	international application: receiving Office	
item (1) 17 APRIL 1998 (17/04/98)	2,235,119	CA			
item (2)					
item (3)					

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

\* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

**Box No. VII INTERNATIONAL SEARCHING AUTHORITY**

**Choice of International Searching Authority (ISA)**  
(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

**Request to use results of earlier search; reference to that search** (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

**Box No. VIII CHECK LIST; LANGUAGE OF FILING**

This international application contains the following number of sheets:

request : 3

description (excluding sequence listing part) : 37

claims : 5

abstract : 1

drawings :

sequence listing part of description :

Total number of sheets : 46

This international application is accompanied by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No. VI as item(s): 1 to FOLLOW
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other (specify):

**Figure of the drawings** which should accompany the abstract: —

**Language of filing of the international application:** ENGLISH

**Box No. IX SIGNATURE OF APPLICANT OR AGENT**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

MBM & Co. (Margaret S. Swain, Partner)

For receiving Office use only		2. Drawings: <input type="checkbox"/> received: <input checked="" type="checkbox"/> not received:
1. Date of actual receipt of the purported international application: 19 APRIL 1999 (19.04.99)		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. <input checked="" type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

Date of receipt of the record copy by the International Bureau:

For International Bureau use only



## PATENT COOPERATION TREATY

MARUSYK MILLER &amp; SWAIN

MAR 23 2000

From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

MBM & CO.  
P.O. Box 809, Station B  
Ottawa, Ontario K1P 5P9  
CANADA

RECEIVED  
DOCKETING  
CALL UP: 5/16/00  
DUE DATE: 6/16/00  
BY: *KID*

PCT  
RECEIVED

WRITTEN OPINION

(PCT Rule 66)

Date of mailing  
(day/month/year)

16. 03. 00

Applicant's or agent's file reference

379-110PCT

REPLY DUE

within 3 month(s)

from the above date of mailing

International application No.

PCT/CA99/00311

International filing date (day/month/year)

19/04/1999

Priority date (day/month/year)

17/04/1998

International Patent Classification (IPC) or both national classification and IPC

C07C229/28

Applicant

CURRY, Kenneth et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain document cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

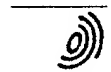
**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

**If no reply is filed,** the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **17/08/2000.**

Name and mailing address of the international preliminary examining authority:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Butkowskyj-Walkiw, T

Formalities officer (incl. extension of time limits)

Roche, S

Telephone No. +49 89 2399 8031







**I. Basis of the opinion**

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

**Description, pages:**

1-36 as received on 28/07/1999 with letter of 09/07/1999

**Claims, No.:**

1-10 as received on 28/07/1999 with letter of 09/07/1999

**Drawings, sheets:**

1 as received on 28/07/1999 with letter of 09/07/1999

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-10
Inventive step (IS)	Claims	1-10
Industrial applicability (IA)	Claims	7

2. Citations and explanations

see separate sheet



**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)  
and / or
2. Non-written disclosures (Rule 70.9)  
see separate sheet

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

see separate sheet

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet



V.

In the light of the documents cited in the search report the present claims 1-10 can be considered as being novel (Art. 33(2) PCT).

Further, the present claims 1-10 can be considered as being inventive (Art. 33(3) PCT) as the object of the present application, namely to provide compounds that demonstrate activity at the various metabotropic glutamate receptors (mGluRs), and the presently claimed solution have not been suggested by any of the cited prior art documents. D1 (PELLICCIARI et al, Asymmetric Synthesis of Enantiomerically pure (2S,1'S,2'S,3'R)-Phenylcarboxycyclopropylglycine, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 18, pages 2243-2246, 1996) which can be considered as closest prior art document refers to cyclopropyl analogs and in the light of this teaching it was not obvious for a skilled person to arrive at the present subject-matter.

For the assessment of the present claim 7 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI.

The present application claims priority rights from 17/4/98. The priority document pertaining to the present application was not available at the time of establishing this first written opinion. Hence it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document PELLICCIARI et al: "Synthesis and preliminary evaluation of (S)-2-(4'-carboxycubyl)glycine, a new selective mGluR1 antagonist" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 12, 16/6/98, pages 1569-1574, cited in the search report would become very relevant in the assessment of the patentability of the present application.

VII.

Claim 3 which refers to claim 1 is inconsistent with claim 1 as it claims  $R_2 = \text{COOH}$ .  
Further, claim 4 which refers to claim 1 is inconsistent with claim 1 as it claims  $R_4 =$



NH<sub>2</sub>.

VIII.

The term "aliphatic" (claim 1) is too broad in scope and therefore too unclear (Art. 6 PCT).

Further, expressions as "the like" and "about" with reference to ranges are too unclear. In claims 5,8-10 the definition of the substituents should be included or a reference to claim 1 should be incorporated.





IPEA/

## CHAPTER II

under Article 31 of the Patent Cooperation Treaty:  
The undersigned requests that the international application specified below be the subject of  
international preliminary examination according to the Patent Cooperation Treaty and  
hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
<b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>	
Applicant's or agent's file reference 379-110PCT	
International application No. PCT/CA99/00311	International filing date (day/month/year) 19 April 1999
(Earliest) Priority date (day/month/year) 17 April 1998	
Title of invention <b>CUBANE DERIVATIVES AS METABOTROPIC GLUTAMATE RECEPTOR          ANTAGONISTS AND PROCESS FOR THEIR PREPARATION</b>	
<b>Box No. II APPLICANT(S)</b>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
CURRY, Kenneth 1176 East King Edward Avenue Vancouver, British Columbia V5V 2G2 Canada	
Telephone No.:	
Facsimile No.:	
Teleprinter No.:	
State (that is, country) of nationality: CA	State (that is, country) of residence: CA
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
PAJOUHESH, Hassan Suite 601 1020 Harwood Street Vancouver, British Columbia V6E 1S1	
State (that is, country) of nationality: CA	State (that is, country) of residence: CA
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
State (that is, country) of nationality:	State (that is, country) of residence:
<input type="checkbox"/> Further applicants are indicated on a continuation sheet.	



**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*MBM & CO.  
P.O. Box 809, Station B  
Ottawa, Ontario  
K1P 5P9  
Canada

Telephone No.:

(613) 567-0762

Facsimile No.:

(613) 563-7671

Teleprinter No.:

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:\***

1. The applicant wishes the international preliminary examination to start on the basis of:

☐ the international application as originally filed

the description

☐ as originally filed☐ as amended under Article 34

the claims

☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34

the drawings

☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

\* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

None



## Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- |  |   |        |
|--|---|--------|
| 1. translation of international application                              | : | sheets |
| 2. amendments under Article 34   | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19  | : | sheets |
| 5. letter  | : | sheets |
| 6. other (specify)   | : | sheets |

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Examining Authority use only

received                      not received

<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

- |  |   |
|--|---|
| 1. <input type="checkbox"/> fee calculation sheet  | 4. <input type="checkbox"/> statement explaining lack of signature                                  |
| 2. <input type="checkbox"/> separate signed power of attorney                            | 5. <input type="checkbox"/> nucleotide and or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 6. <input type="checkbox"/> other (specify):  |

## Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

MBM & CO. (Margaret Swain, Partner)

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

